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(54) **ANTIALLERGIC TRIAZOLO(PYRROLO, THIENO OR FURANO)AZEPINE DERIVATIVES**

ANTIALLERGISCH TRIAZOLO (PYRROLO, THIENO ODER FURANO) AZEPINDERIVATE

DERIVES D'AZEPINE TRIAZOLO(PYRROLO, THIENO OU FURANO)

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(56) References cited:

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Remarks:

The file contains technical information submitted
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this specification

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EP 0 675 889 B1

Description

[0001] The present invention is concerned with novel triazolo(pyrrolo, thieno or furano)azepine derivatives having antiallergic activity.

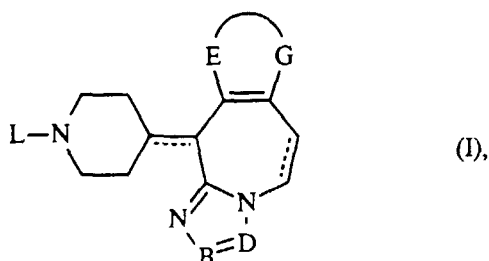
[0002] In EP-A-0,339,978 there are described (benzo- or pyrido)cyclohepta heterocyclics which are useful as PAF antagonists, antihistaminics and/or anti-inflammatory agents.

[0003] In the J. Med. Chem., 26 (1983), 974-980 there are described some 1-methyl-4-piperidinylidene-9-substituted pyrrolo[2,1-b][3]benzazepine derivatives having neuroleptic properties.

[0004] In WO-A-9206981 there are described substituted imidazobenzazepines and imidazopyridoazepines having antiallergic and anti-inflammatory activity.

[0005] The compounds of the present invention differ structurally from the cited art-known compounds by the fact that the central 7-membered ring invariably contains a nitrogen atom of a fused triazole ring, and by their favourable antiallergic activity.

[0006] The present invention is concerned with novel triazolo(pyrrolo, thieno or furano)azepines of formula



the pharmaceutically acceptable addition salts and stereochemically isomeric forms thereof, wherein each of the dotted lines independently represents an optional bond;

-E-G- is a bivalent radical of formula



or



X represents O, S or NR³;

R³ represents hydrogen, C₁₋₆alkyl or C₁₋₄alkylcarbonyl;

R¹ and R² each independently represent hydrogen, C₁₋₄alkyl, halo, ethenyl substituted with hydroxycarbonyl or C₁₋₄alkyloxycarbonyl, hydroxyC₁₋₄alkyl, formyl, hydroxycarbonyl or hydroxycarbonylC₁₋₄alkyl;

-B=D- is a bivalent radical of formula



or



R⁴ represents hydrogen or C₁₋₄alkyl;

R⁵ represents hydrogen or C₁₋₄alkyl;

L represents hydrogen; C₁₋₆alkyl; C₁₋₆alkyl substituted with one substituent selected from the group consisting of hydroxy, C₁₋₄alkyloxy, hydroxycarbonyl, C₁₋₄alkyloxycarbonyl, C₁₋₄alkyloxycarbonylC₁₋₄alkyloxy, hydroxycarbonylC₁₋₄alkyloxy, C₁₋₄alkylaminocarbonylamino, C₁₋₄alkylaminothiocarbonylamino, aryl and aryloxy; C₁₋₆alkyl substituted with both hydroxy and aryloxy; C₃₋₆alkenyl; C₃₋₆alkenyl substituted with aryl; wherein each aryl is phenyl or phenyl substituted with halo, cyano, hydroxy, C₁₋₄alkyl, C₁₋₄alkyloxy or aminocarbonyl; or,

L represents a radical of formula

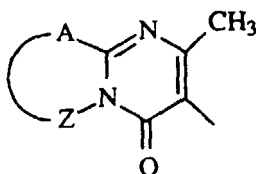
-Alk-Y-Het¹ (c-1),

-Alk-NH-CO-Het² (c-2)

5 or

-Alk-Het³ (c-3) ;

10 Alk wherein
Y represents C₁₋₄alkanediyl;
represents O, S or NH ;
Het¹, Het² and Het³ each represent furanyl, thienyl, oxazolyl, thiazolyl or imidazolyl each optionally substituted with one or two C₁₋₄alkyl substituents; pyrrolyl or pyrazolyl optionally substituted with formyl, hydroxyC₁₋₄alkyl, hydroxycarbonyl, C₁₋₄alkyloxycarbonyl or with one or two C₁₋₄alkyl substituents; thiadiazolyl or oxadiazolyl optionally substituted with amino or C₁₋₄alkyl; pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl each optionally substituted with C₁₋₄alkyl, C₁₋₄alkyloxy, amino, hydroxy or halo; and Het³ may also represent 4,5-dihydro-5-oxo-1H-tetrazolyl substituted with C₁₋₄alkyl, 2-oxo-3-oxazolidinyl, 2,3-dihydro-2-oxo-1H-benzimidazol-1-yl or a radical of formula



wherein
A-Z represents S-CH=CH, S-CH₂-CH₂, S-CH₂-CH₂-CH₂, CH=CH-CH=CH, or CH₂-CH₂-CH₂-CH₂.

30

[0007] As used in the foregoing definitions halo defines fluoro, chloro, bromo and iodo; C₁₋₄alkyl defines straight and branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, for example, methyl, ethyl, propyl, 1-methylethyl, butyl, 1-methylpropyl, 2-methylpropyl and 1,1-dimethylethyl; C₁₋₆alkyl defines C₁₋₄alkyl radicals as defined hereinbefore and the higher homologs thereof having from 5 to 6 carbon atoms such as, for example, pentyl and hexyl; C₃₋₆alkenyl defines straight and branched chain hydrocarbon radicals containing one double bond and having from 3 to 6 carbon atoms such as, for example, 2-propenyl, 2-butenyl, 3-butenyl, 2-methyl-2-propenyl, 2-pentenyl, 3-pentenyl, 3,3-dimethyl-2-propenyl and hexenyl, C₁₋₄alkanediyl defines bivalent straight or branched chain hydrocarbon radicals containing from 1 to 4 carbon atoms such as, for example, methylene, 1,1-ethanediyl, 1,2-ethanediyl, 1,3-propanediyl and 1,4-butanediyl.

40 **[0008]** The term pharmaceutically acceptable addition salt as used hereinbefore defines the non-toxic, therapeutically active addition salt forms which the compounds of formula (I) may form. The compounds of formula (I) having basic properties may be converted into the corresponding therapeutically active, non-toxic acid addition salt forms by treating the free base form with a suitable amount of an appropriate acid following conventional procedures. Examples of appropriate acids are for example, inorganic acids, for example, hydrohalic acid, e.g. hydrochloric, hydrobromic and the like acids, sulfuric acid, nitric acid and phosphoric acid; or organic acids, such as, for example, acetic, propanoic, hydroxyacetic, 2-hydroxypropanoic, 2-oxopropanoic, ethanedioic, propanedioic, butanedioic, (Z)-2-butenedioic, (E)-2-butenedioic, 2-hydroxybutanedioic, 2,3-dihydroxybutanedioic, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic and 4-amino-2-hydroxybenzoic.

50 **[0009]** The compounds of formula (I) having acidic properties may be converted in a similar manner into the corresponding therapeutically active, non-toxic base addition salt forms. Examples of such base addition salt forms are, for example, the sodium, potassium, calcium salts, and also the salts with pharmaceutically acceptable amines such as, for example, ammonia, alkylamines, benzathine, N-methyl-D-glucamine, hydrabamine, amino acids, e.g. arginine, lysine. The term pharmaceutically acceptable addition salts also comprises the solvates which the compounds of formula (I) may form, e.g. the hydrates and alcoholates.

55 **[0010]** The term stereochemically isomeric forms as used herein before defines the possible different isomeric as well as conformational forms which the compounds of formula (I) may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically and conformation-

ally isomeric forms, said mixtures containing all diastereomers, enantiomers and/or conformers of the basic molecular structure. All stereochemically isomeric forms of the compounds of formula (I) both in pure form or in admixture with each other are intended to be embraced within the scope of the present invention.

[0011] Some compounds of the present invention may exist in different tautomeric forms and all such tautomeric forms are intended to be included within the scope of the present invention.

[0012] An interesting group of compounds of formula (I) comprises those compounds of formula (I) wherein R^1 , R^2 , R^4 and R^5 represent hydrogen.

[0013] Another group of interesting compounds of formula (I) are those wherein X represents S or NCH_3 .

[0014] Further interesting compounds of formula (I) are those wherein L is C_{1-4} -alkyl.

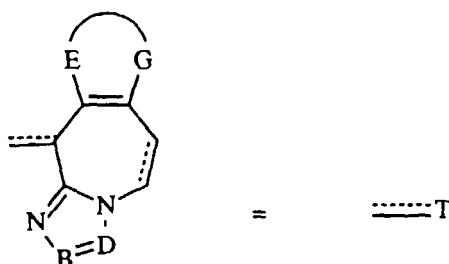
[0015] The most preferred compounds are :

5,6,7,10-tetrahydro-7-methyl-10-(1-methyl-4-piperidinylidene)pyrrolo[3,2-d][1,2,4]triazolo[1,5-a]azepine;

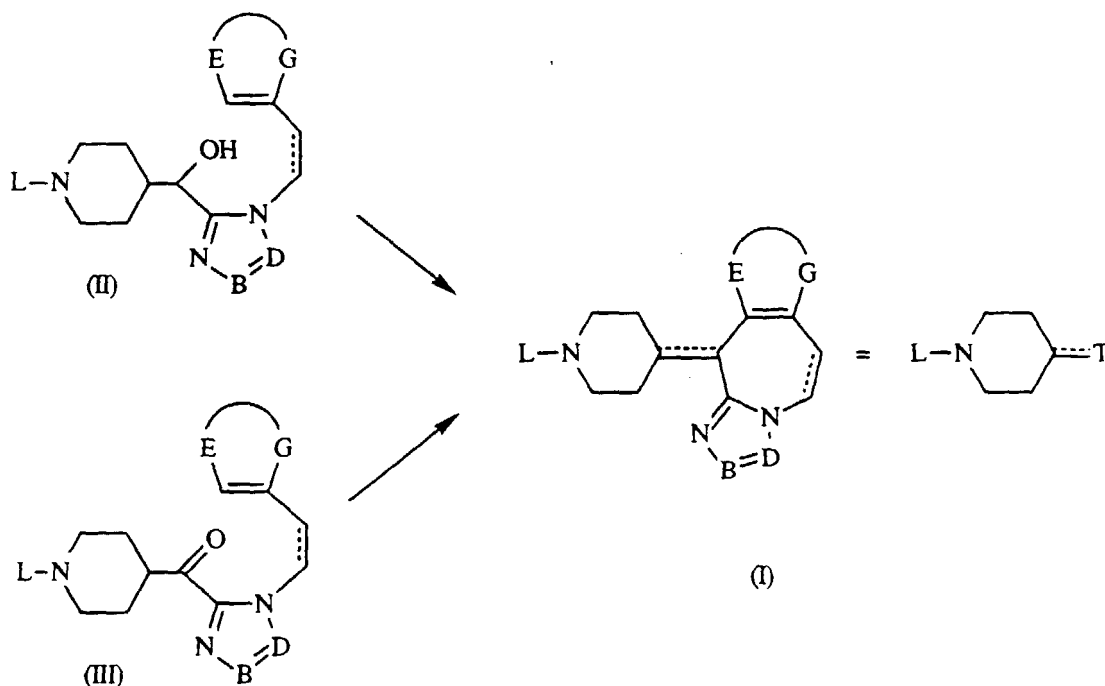
10-(1-methyl-4-piperidinylidene)-10H-thieno[3,2-d]-1,2,4-triazolo[4,3-a]azepine; and

6,10-dihydro-10-(1-methyl-4-piperidinylidene)-5H-thieno[2,3-d][1,2,4]triazolo[1,5-a]azepine, the stereoisomers and the pharmaceutically acceptable acid-addition salts thereof.

[0016] In the following paragraphs there are described different ways of preparing the compounds of formula (I). In order to simplify the structural formulae of the compounds of formula (I) and the intermediates intervening in their preparation, the triazolo(pyrrolo, thieno or furano)azepine moiety will be represented by the symbol T hereinafter.



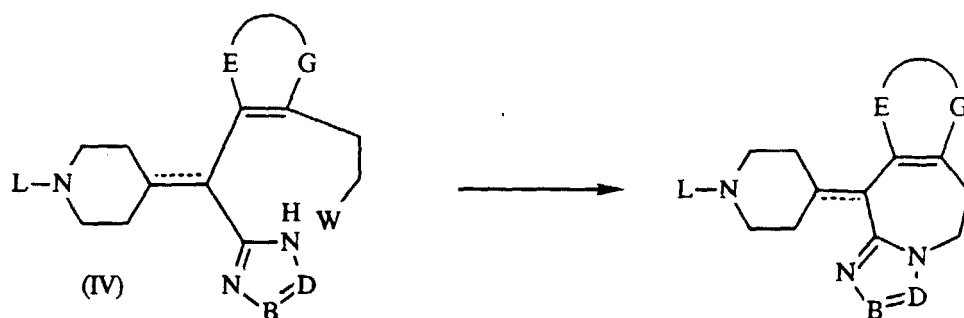
[0017] The compounds of formula (I) can be prepared by cyclizing an alcohol of formula (II) or a ketone of formula (III).



[0018] Said cyclization reaction is conveniently conducted by treating the intermediate of formula (II) or (III) with an appropriate acid, thus yielding a reactive intermediate which cyclizes to a compound of formula (I). Appropriate acids are, for example, strong acids, in particular superacid systems, e.g. methanesulfonic acid, trifluoromethanesulfonic acid, trifluoroacetic acid, methanesulfonic acid / boron trifluoride, hydrofluoric acid / boron trifluoride, or Lewis acids, e.g. aluminum chloride, tin(IV)chloride, trimethylsilyl iodide and phosphorylchloride. Obviously, only those compounds of formula (I) wherein L is stable under the given reaction conditions can be prepared according to the above reaction procedure. In case of superacids the reaction is preferably conducted in an excess of said acid; in case of a Lewis acid such as, e.g. tin(IV)chloride, the reaction can conveniently be conducted in a reaction-inert solvent such as, for example, a halogenated hydrocarbon, e.g. dichloromethane or 1,2-dichloroethane.

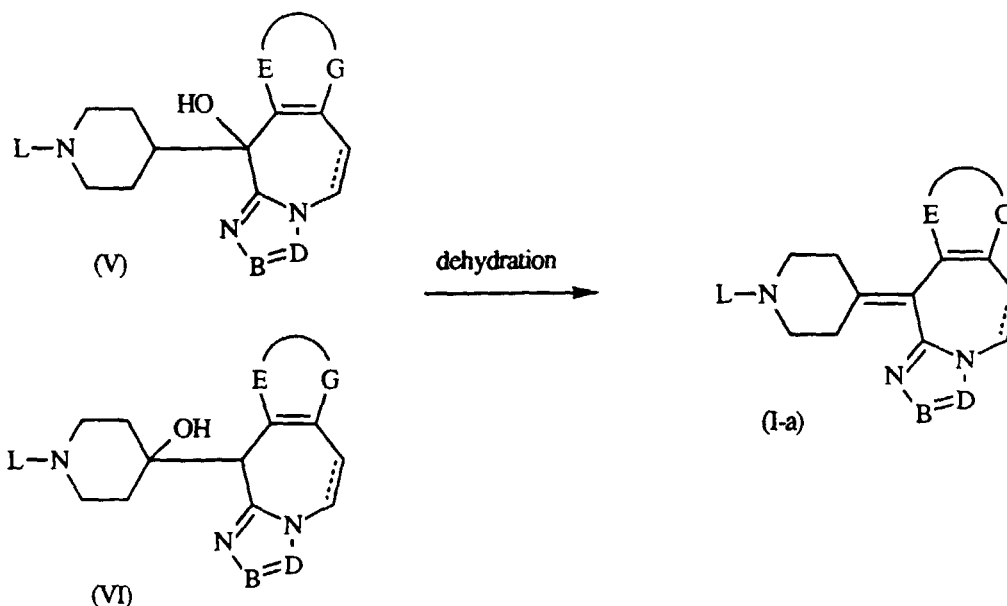
[0019] In the foregoing and following preparations, the reaction mixture is worked up following an-known methods and the reaction product is isolated and, if necessary, further purified.

[0020] The compounds of formula (I) wherein the central ring of the tricyclic moiety does not contain an optional bond may also be prepared by cyclizing an intermediate of formula (IV).

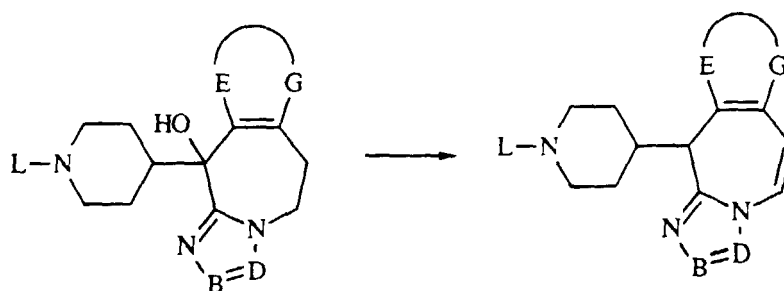


[0021] In formula (IV) and hereinafter W represents an appropriate leaving group such as, for example, halo, e.g. chloro and bromo; or a sulfonyloxy group such as, for example, methanesulfonyloxy, 4-methylbenzenesulfonyloxy. Said cyclization reaction can conveniently be conducted in a reaction-inert solvent such as, for example, an aromatic hydrocarbon, an alkanol, a ketone, an ether, a dipolar aprotic solvent, or a mixture of such solvents. The addition of an appropriate base such as, for example, an alkali or an earth alkaline metal carbonate, hydrogen carbonate, alkoxide, hydride, amide, hydroxide or oxide; or an organic base, may be utilized to pick up the acid which is liberated during the course of the reaction. In some instances the addition of an iodide salt, preferably an alkali metal iodide, is appropriate. Somewhat elevated temperatures and stirring may enhance the rate of the reaction.

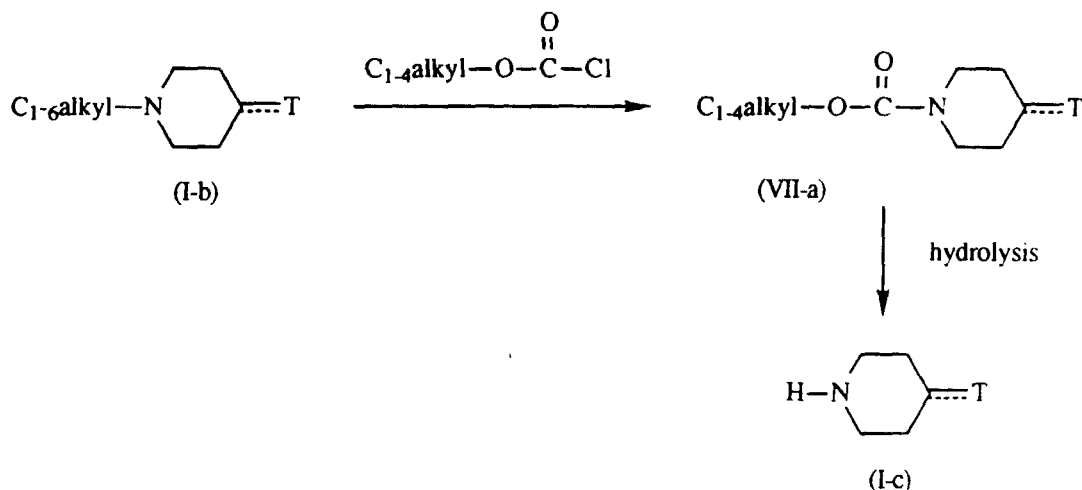
[0022] Alternatively, the compounds of formula (I) wherein a double bond exists between the piperidiny and the triazolo(pyrrolo, thieno or furano)azepine moiety, said compounds being represented by formula (I-a), can be prepared by dehydrating an alcohol of formula (V) or (VI).



[0023] Said dehydration reaction can conveniently be conducted employing conventional dehydrating reagents following art-known methodologies. Appropriate dehydrating reagents are, for example, acids, e.g. sulfuric acid, phosphoric acid, hydrochloric acid, methanesulfonic acid, carboxylic acids, e.g. acetic acid, trifluoroacetic acid and mixtures thereof; anhydrides, e.g. acetic anhydride and phosphorus pentoxide; other suitable reagents, e.g. zinc chloride, thionyl chloride, boron trifluoride etherate, phosphoryl chloride pyridine, potassium bisulfate, potassium hydroxide or phosphoryl chloride. Optionally, said dehydration reaction is conducted in a reaction-inert solvent such as, for example, a halogenated hydrocarbon, e.g. dichloromethane. In some instances said dehydration reaction may require heating the reaction mixture, more particularly up to the reflux temperature. Again, only those compounds of formula (I-a) wherein L is stable under the given reaction conditions can be prepared according to the above reaction procedure. Particularly noteworthy is the fact that the latter reaction when performed on intermediate (V) wherein the dotted line does not represent an optional bond, in some instances may also yield a compound with a double bond in the tricyclic moiety and a single bond bridging the tricyclic moiety and the piperidine :



[0024] The compounds of formula (I) wherein L is C₁₋₆alkyl, said compounds being represented by the formula (I-b), can be converted into the compounds of formula (I) wherein L is hydrogen, said compounds being represented by the formula (I-c), in a number of manners. A first method involves dealkylating - carbonylating the compounds of formula (I-b) with a C₁₋₄alkylchloroformate and subsequently hydrolyzing the thus obtained compound of formula (VII-a).

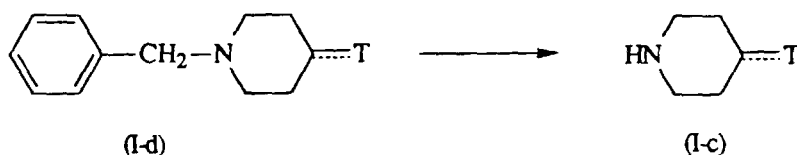


[0025] The reaction with the C_{1-4} alkylchloroformate is conveniently conducted by stirring and heating the starting material (I-b) with the reagent in an appropriate solvent and in the presence of a suitable base. Appropriate solvents are, for example, aromatic hydrocarbons, e.g. methylbenzene, dimethylbenzene, chlorobenzene; ethers, e.g. 1,2-dimethoxyethane, and the like solvents. Suitable bases are, for example, alkali or earth alkaline metal carbonates, hydrogen carbonates, hydroxides, or organic bases such as *N,N*-diethylethanamine and *N*-(1-methylethyl)-2-propanamine.

The compounds of formula (VII-a) are hydrolyzed in acidic or basic media following conventional methods. For example, concentrated acids such as hydrobromic, hydrochloric acid or sulfuric acid can be used, or alternatively bases such as alkali metal or earth alkaline metal hydroxides, e.g. sodium hydroxide, potassium hydroxide and the like, in water, an alkanol or a mixture of water-alkanol may be used. Suitable alkanols are methanol, ethanol and 2-propanol. In order to enhance the rate of the reaction it is advantageous to heat the reaction mixture, in particular up to the reflux temperature.

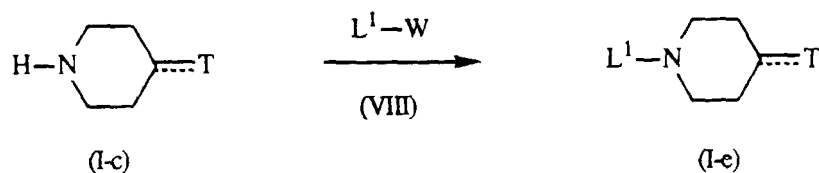
[0026] The compounds of formula (I-b) may also be converted directly into the compounds of formula (I-c) by stirring and heating them with an α -halo C_{1-4} alkyl chloroformate in an appropriate solvent such as, for example, a halogenated hydrocarbon, e.g. dichloromethane, trichloromethane; an aromatic hydrocarbon, e.g. methylbenzene, dimethylbenzene; an ether, e.g. 1,2-dimethoxyethane; an alcohol, e.g. methanol, ethanol, 2-propanol, optionally in the presence of a base such as, for example, an alkali or earth alkaline metal carbonate, hydrogen carbonate, hydroxide or an amine, e.g. *N,N*-diethylethanamine and *N*-(1-methylethyl)-2-propanamine.

[0027] The compounds of formula (I-c) can also be prepared by debenzylating a compound of formula (I-d) by catalytic hydrogenation in the presence of hydrogen and an appropriate catalyst in a reaction-inert solvent.



[0028] A suitable catalyst in the above reaction is, for example, platinum-on-charcoal or palladium-on-charcoal. An appropriate reaction-inert solvent for said debenzylation reaction is, for example, an alcohol, e.g. methanol, ethanol, 2-propanol, and the like, an ester, e.g. ethyl acetate and the like, an acid, e.g. acetic acid.

[0029] The compounds of formula (I) wherein L is other than hydrogen, said compounds being represented by formula (I-e) and said L by L^1 , can be prepared by *N*-alkylating the compounds of formula (I-c) with a reagent of formula $\text{L}^1\text{-W}$ (VIII).



[0030] Said N-alkylation reaction can conveniently be conducted in a reaction-inert solvent such as, for example, an aromatic hydrocarbon, an alkanol, a ketone, an ether, a dipolar aprotic solvent, a halogenated hydrocarbon, or a mixture of such solvents. The addition of an appropriate base such as, for example, an alkali or an earth alkaline metal carbonate, hydrogen carbonate, alkoxide, hydride, amide, hydroxide or oxide, or an organic base, may be utilized to pick up the acid which is liberated during the course of the reaction. In some instances the addition of an iodide salt, preferably an alkali metal iodide, is appropriate. Somewhat elevated temperatures and stirring may enhance the rate of the reaction. Alternatively, said N-alkylation may be carried out by applying art-known conditions of phase transfer catalysis reactions.

[0031] The compounds of formula (I) wherein L is C₁₋₆alkyl or substituted C₁₋₆alkyl can also be prepared by reductive N-alkylation of the compounds of formula (I-c) following art-known procedures. The compounds of formula (I) wherein L is C₁₋₆alkyl or substituted C₁₋₆alkyl can further be prepared by the addition reaction of the compounds of formula (I-c) with a suitable alkene following art-known procedures.

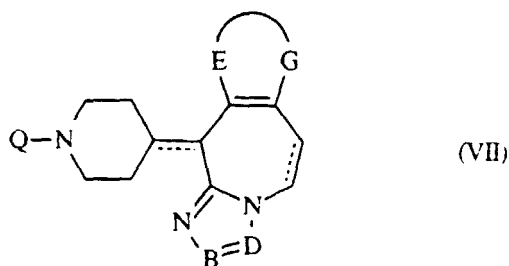
The compounds of formula (I) wherein L is C₁₋₆alkyl substituted with hydroxy can be prepared by reacting a compound of formula (I-c) with a suitable epoxide following art-known procedures.

[0032] The compounds of formula (I) with a double bond in the tricyclic moiety and/or a double bond bridging the tricyclic moiety and the piperidine may be reacted into compounds of formula (I) with a single bond at either one or both of the beforementioned sites following art-known reduction procedures.

[0033] The compounds of formula (I) may further be converted into each other following art-known functional group transformation procedures.

[0034] For example, the compounds of formula (I) wherein R¹ or R² is formyl may be prepared by reacting the corresponding compound of formula (I) wherein R¹ or R² is hydrogen with e.g. N,N-dimethylformamide in the presence of a suitable reagent, e.g. phosphoryl chloride. The compounds of formula (I) wherein R¹ or R² is formyl may be further converted in the corresponding hydroxymethyl compounds following art-known reduction procedures.

[0035] The compounds of formula (VII-a) intervening in the preparations described hereinbefore are novel and have especially been developed for use as intermediates in said preparations. Consequently, the present invention also relates to novel compounds of formula



the addition salts and the stereochemically isomeric forms thereof, wherein

each of the dotted lines independently represents an optional bond;

-E-G- and -B=D- are as defined for the compounds of formula (I); and

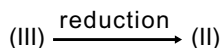
Q represents C₁₋₆alkyloxycarbonyl, C₁₋₄alkylcarbonyl or C₁₋₆alkyl substituted with halo, cyano, amino, or methylsulfonyloxy.

[0036] Particularly interesting compounds of formula (VII) are those wherein Q represents C₁₋₆alkyloxycarbonyl, the addition salts and the stereochemically isomeric forms thereof.

[0037] In the following paragraphs there are described several methods of preparing the starting materials

employed in the foregoing preparations.

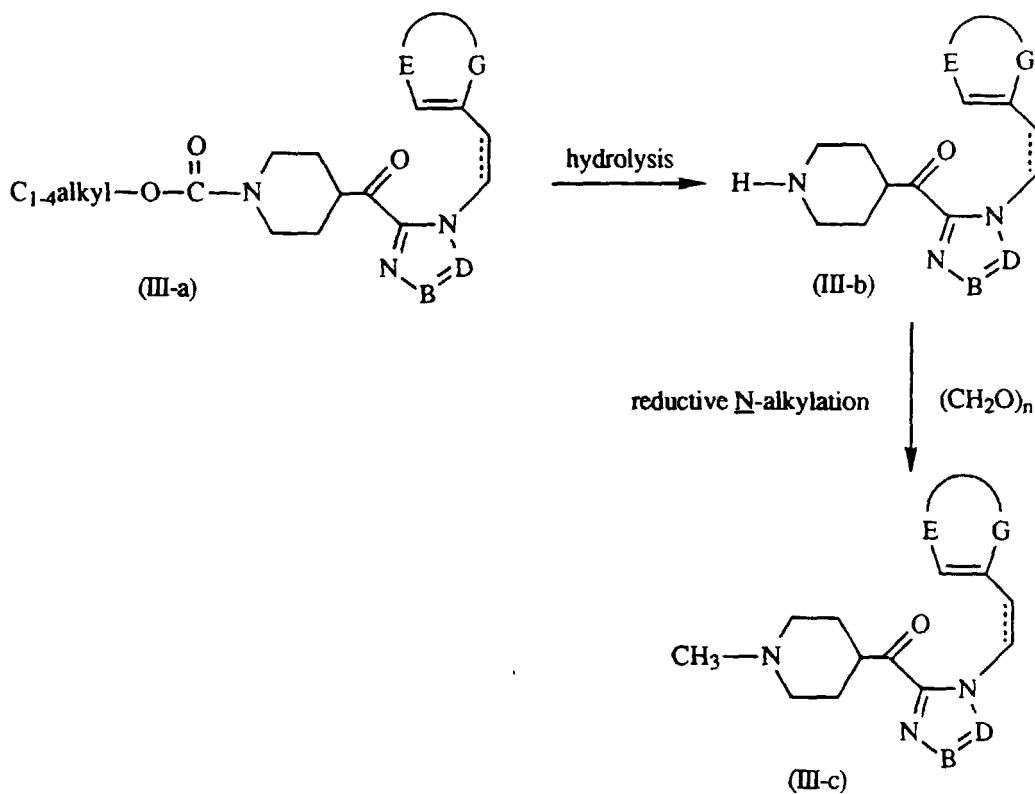
[0038] The intermediates of formula (II) can be prepared from the corresponding ketones of formula (III) by reduction.



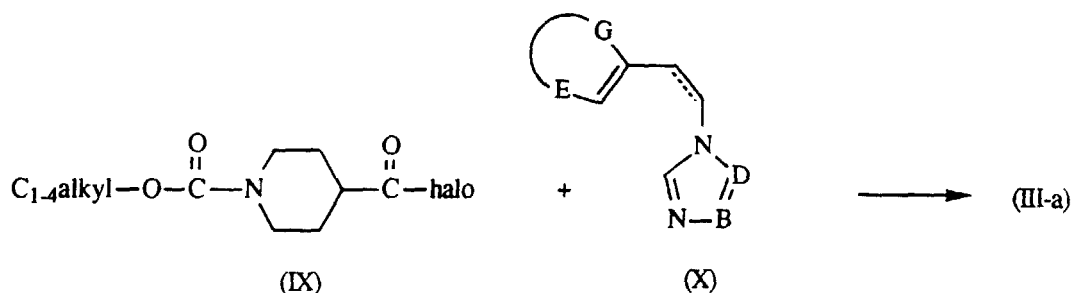
[0039] Said reduction can conveniently be conducted by reacting the starting ketone (III) with hydrogen in a solvent such as, for example, an alcohol, e.g. methanol, ethanol; an acid, e.g. acetic acid; an ester, e.g. ethyl acetate; in the presence of a hydrogenation catalyst, e.g. palladium-on-charcoal, platinum-on-charcoal, Raney Nickel. In order to enhance the rate of the reaction, the reaction mixture may be heated and, if desired, the pressure of the hydrogen gas may be raised.

[0040] Alternatively, the alcohols of formula (II) can also be prepared by reducing the ketones (III) with a reducing agent such as, for example, lithium aluminum hydride, sodium borohydride and sodium cyanoborohydride in a suitable solvent such as, for example, an ether, e.g. 1,1'-oxybisethane, tetrahydrofuran and the like; an alcohol, e.g. methanol and ethanol.

[0041] The ketones of formula (III) wherein L represents hydrogen are prepared by hydrolysis of a carbamate of formula (III-a) in acidic or basic media following conventional methods as described hereinbefore for the preparation of compounds of formula (I-c) from the compounds of formula (I-b).



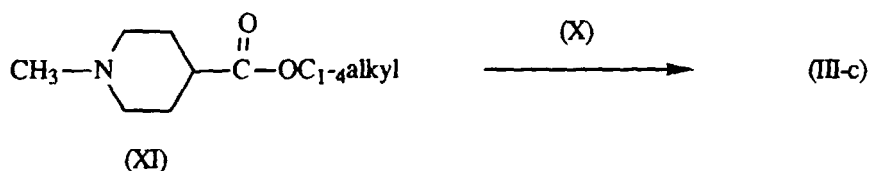
[0042] The intermediates of formula (III-a) can be prepared by reacting an acid halide of formula (IX) with a triazole derivative of formula (X).



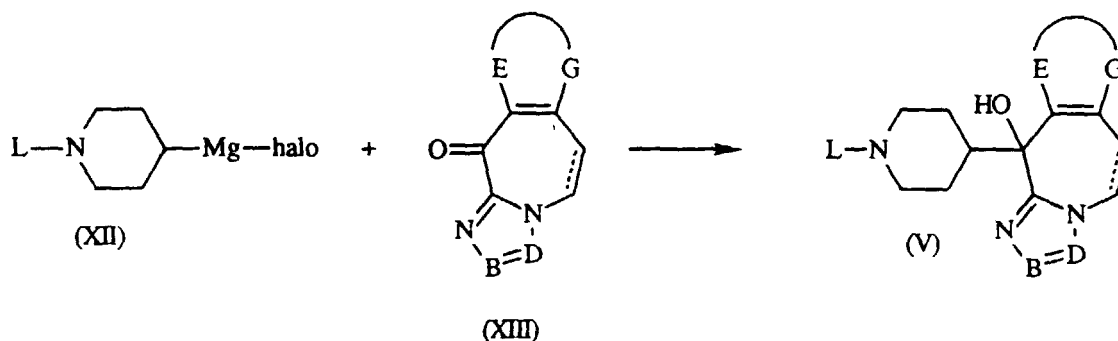
[0043] Said reaction is conveniently conducted by stirring and heating the reactants in the presence of a base such as, for example, an amine, e.g. *N,N*-diethylethanamine and *N*-methyldmorpholine, in a suitable solvent such as, for example, pyridine, acetonitrile or a mixture thereof.

[0044] The intermediates of formula (III-c) can also be prepared from an ester of formula (XI) by reaction with a triazole of formula (X) in the presence of a strong base such as, for example, methyl lithium, butyl lithium, sodium amide, a dialkyl lithium amide, e.g. diisopropyl lithium amide, or a mixture thereof, in a suitable reaction-inert solvent, e.g. tetrahydrofuran, hexane and methylbenzene, or a mixture thereof.

[0045] Said reaction is conveniently conducted at low temperatures. For example the reagent (X) may be stirred at a temperature between -80°C to -40°C , whereupon the strong base is added. Subsequently the ester is added and the reaction mixture is allowed to warm up gently to room temperature.



[0046] The intermediates of formula (V) can be prepared by addition of a Grignard reagent (XII) to a ketone of formula (XIII) in a reaction-inert solvent, e.g. tetrahydrofuran.



[0047] The tricyclic ketones of formula (XIII) in turn are prepared from intermediates of formula (XIV) by oxidation with a suitable oxidizing reagent in a reaction-inert solvent.



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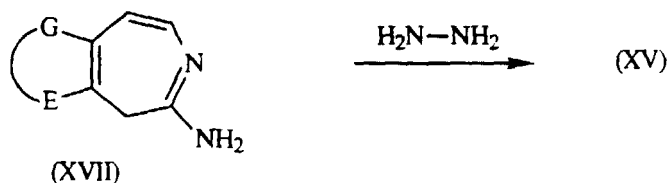
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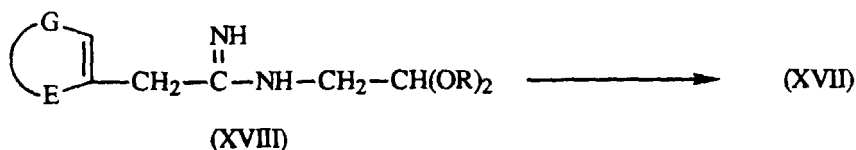
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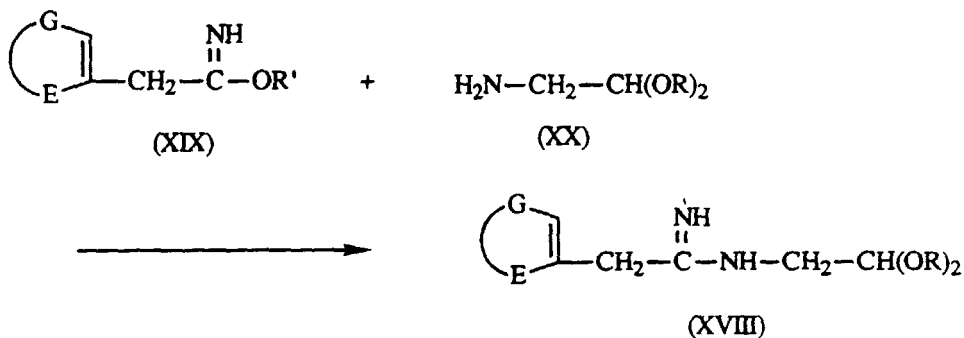


10 [0052] The intermediates of formula (XVII) can be prepared by reacting an intermediate of formula (XVIII) or a derivative thereof, in an acidic medium. In (XVIII) R represents C_{1-4} alkyl or both radicals R taken together represent C_{2-6} alkanediyl, e.g. 1,2-ethanediyl, 1,3-propanediyl, 2,2-dimethyl-1,3-propanediyl.

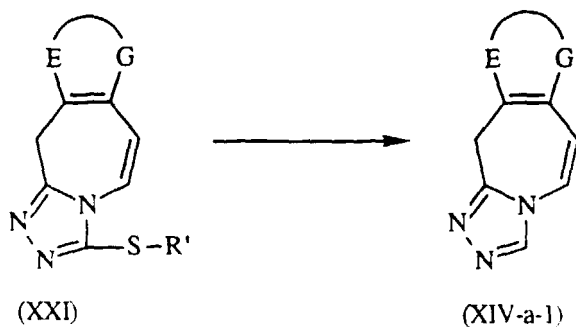


25 [0053] The above cyclization reaction is conveniently conducted by stirring the starting material (XVIII) in a carboxylic acid, such as, for example, acetic acid, propanoic acid and the like, optionally in admixture with a mineral acid such as, for example, hydrobromic acid and methanesulfonic acid.

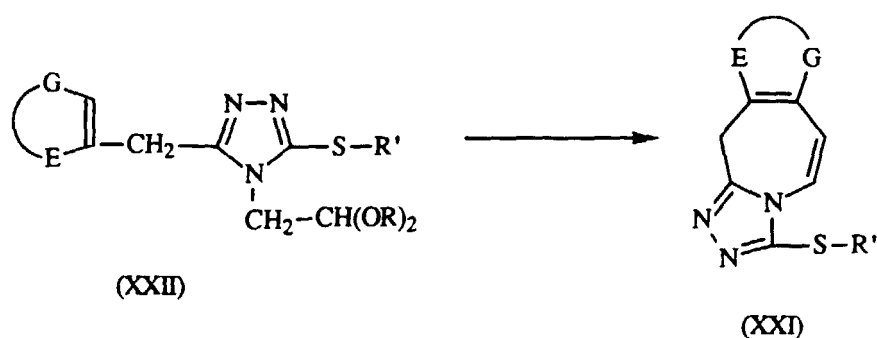
The intermediates of formula (XVIII) can be prepared by reacting an intermediate of formula (XIX) or a derivative thereof, wherein R' is C_{1-4} alkyl, with a reagent of formula (XX) in a reaction-inert solvent such as, for example, an ether, e.g. 1,2-dimethoxyethane and tetrahydrofuran.



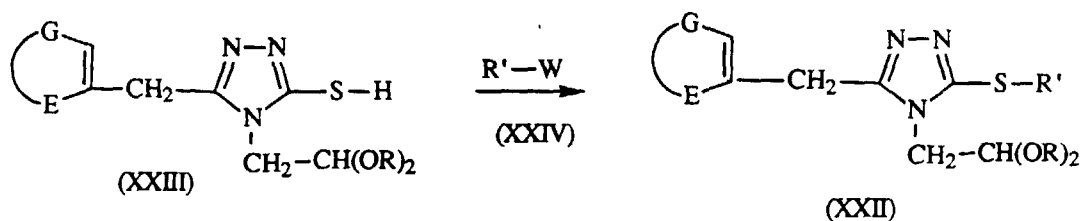
45 [0054] Alternatively, the intermediates of formula (XIV-a-1) can be prepared by reacting an intermediate of formula (XXI) under hydrogen pressure in the presence of a suitable catalyst, e.g. Raney nickel and the like, in a reaction-inert solvent, e.g. methanol and ethanol.



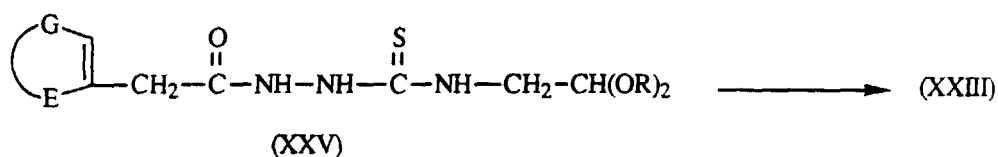
[0055] The intermediates of formula (XXI) can be prepared by the cyclization of an intermediate of formula (XXII) in the presence of an acid, e.g. sulfuric acid.



[0056] The intermediates of formula (XXII) can be prepared by the S-alkylation of an intermediate of formula (XXIII) with a reagent of formula $R'-W$ (XXIV) in a reaction-inert solvent, e.g. methanol, ethanol, and the like, optionally in the presence of a base e.g. sodium methoxide.

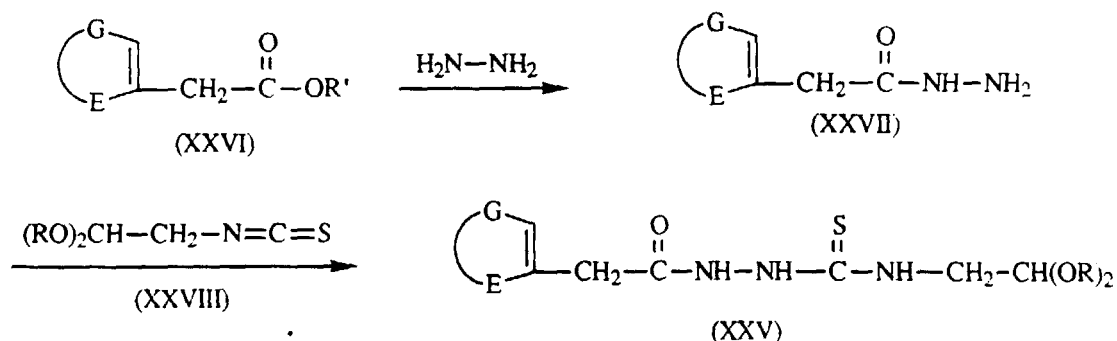


[0057] The intermediates of formula (XXIII) can be prepared by the cyclization of an intermediate of formula (XXV) in the presence of a base, e.g. potassium hydroxide.

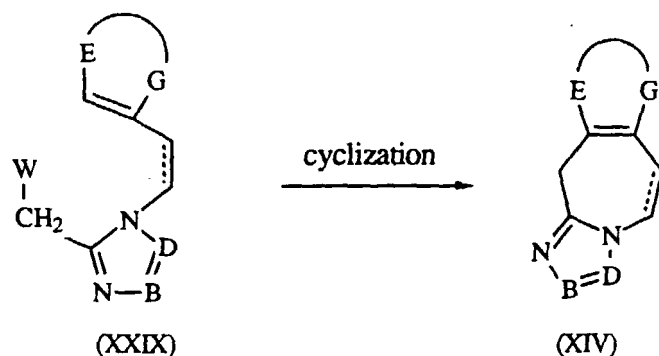


[0058] The intermediates of formula (XXV) can be prepared by reacting an intermediate of formula (XXVI) with

hydrazine or a derivative thereof in a reaction-inert solvent, e.g. ethanol. The resulting intermediate of formula (XXVII) is then further reacted with a reagent of formula (XXVIII) in a reaction-inert solvent, e.g. benzene.

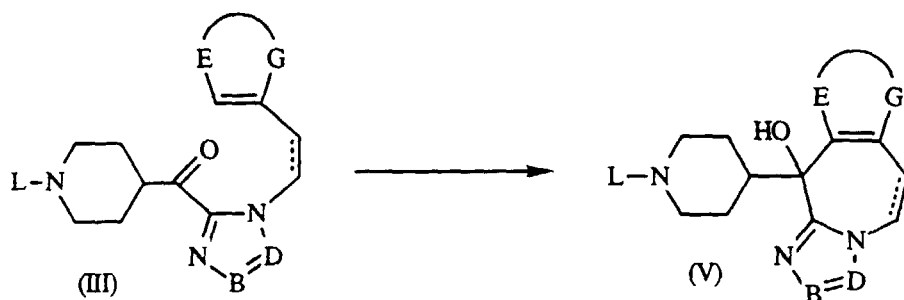


[0059] The intermediates of formula (XIV) can also be prepared from cyclization of an intermediate of formula (XXIX).



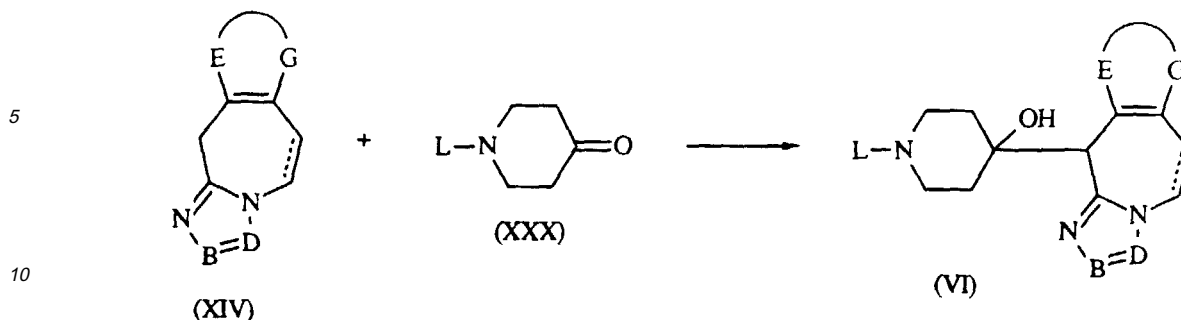
[0060] Said cyclization reaction is conveniently conducted in the presence of a Lewis acid, e.g. aluminum chloride. In some instances it may be appropriate to supplement the reaction mixture with a suitable amount of sodium chloride.

[0061] The intermediates of formula (V) can also be prepared from the cyclization of an intermediate of formula (III) in the presence of an acid in a reaction-inert solvent.

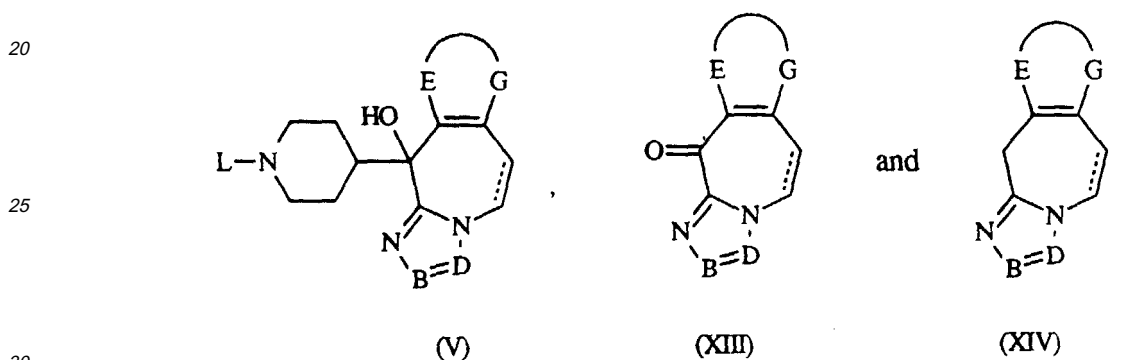


[0062] An appropriate acid in the above reaction is, for example, a Lewis acid, e.g. tin(IV)chloride. A suitable reaction-inert solvent is, for example, a halogenated hydrocarbon, e.g. dichloromethane and 1,2-dichloroethane.

[0063] The intermediates of formula (VI) can be prepared by reaction of a ketone of formula (XXX) with an intermediate of formula (XIV) in the presence of e.g. lithium diisopropyl amide in a reaction-inert solvent, e.g. tetrahydrofuran.



15 **[0064]** The compounds of formula (V), (XIII) and (XIV) intervening in the preparations described hereinbefore are novel and have especially been developed for use as intermediates in said preparations. Consequently, the present invention also relates to novel compounds of formula



the addition salt forms thereof and the stereochemically isomeric forms thereof, wherein L, -B=D- and -E-G- are as defined under formula (I).

35 **[0065]** The compounds of formula (I) and some of the compounds of formula (VII), the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, possess useful pharmacological properties. In particular they are active antiallergic agents, which activity can clearly be demonstrated by the test results obtained in a number of indicative tests. Antihistaminic activity can be demonstrated in 'Protection of Rats from Compound 48/80 - induced Lethality' test (Arch. Int. Pharmacodyn. Ther., 234, 164-176, 1978). The ED₅₀-values for the compounds 2, 3, 4, 5, 7, 8, 9, 14, 16, 19, 23, 26, 27, 29 and 31 were found to be equal or below 0.31 mg/kg.

40 **[0066]** An advantageous feature of the compounds of the present invention resides in their excellent oral activity; the present compounds when administered orally have been found to be practically equivalent with the same being administered subcutaneously.

45 **[0067]** An interesting feature of the present compounds relates to their fast onset of action and the favorable duration of their action.

[0068] In view of their antiallergic properties, the compounds of formula (I), the compounds of formula (VII) and their addition salts are very useful in the treatment of a broad range of allergic diseases such as, for example, allergic rhinitis, allergic conjunctivitis, chronic urticaria and allergic asthma.

50 **[0069]** In view of their useful antiallergic properties the subject compounds may be formulated into various pharmaceutical forms for administration purposes. To prepare the antiallergic compositions of this invention, an effective amount of the particular compound, in base or acid addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for administration orally, rectally, percutaneously, or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils and alcohols in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders and disintegrating agents in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most

advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers and suspending agents may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not introduce a significant deleterious effect on the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on or as an ointment. Addition salts of the subject compounds due to their increased water solubility over the corresponding base form, are obviously more suitable in the preparation of aqueous compositions.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage.

[0070] Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

[0071] The present invention also relates to a method of treating warm-blooded animals suffering from said allergic diseases by administering to said warm-blooded animals an effective antiallergic amount of a compound of formula (I), a compound of formula (VII) or an addition salt form thereof.

In general it is contemplated that an effective antiallergic amount would be from 0.001 mg/kg to 20 mg/kg body weight, and more preferably from 0.01 mg/kg to 5 mg/kg body weight.

[0072] The following examples are intended to illustrate the present invention in all its aspects.

Experimental part

A. Preparation of the intermediate compounds

Example 1

[0073]

a) A mixture of 3-thiopheneethanol methanesulfonate (ester) (0.286 mol), 1,2,4-triazole (0.571 mol) and potassium carbonate (39.47g) in acetonitrile (1100ml) was refluxed overnight. The mixture was filtered off and the filtrate was evaporated. The residue was taken up in water and extracted with dichloromethane. The organic layer was dried (MgSO₄), filtered off and evaporated. The residue (49.08g) was purified by column chromatography over silica gel (eluent : CH₂Cl₂/CH₃OH/NH₄OH 99/1/0.1 to 97/3/0.1) (35-70μm). The pure fractions were collected and evaporated, yielding 42.4g (83%) of 1-[2-(3-thienyl)ethyl]-1H-1,2,4-triazole (interm. 1).

In a similar way there were prepared :

1-[2-(1-methyl-1H-pyrrol-2-yl)ethyl]-1H-1,2,4-triazole (interm. 2); and

1-[2-(5-methyl-2-furanyl)ethyl]-1H-1,2,4-triazole (interm. 27).

b) Butyllithium in hexane (192ml) was added dropwise at -70°C under nitrogen to a solution of N-(1-methylethyl)-2-propanamine (43.4ml) in tetrahydrofuran (400ml) and the mixture was stirred for 30 minutes. A solution of intermediate (1) (0.236 mol) in tetrahydrofuran (50ml) was added dropwise and the mixture was stirred at -70°C for 1 hour. Ethyl 1-methyl-4-piperidinecarboxylate (0.284 mol) in tetrahydrofuran (50ml) was added and after the addition was completed, the mixture was stirred at -70°C for 1 hour. The mixture was brought slowly to room temperature. The mixture was poured into water and extracted with 1,1'-oxybisethane/dichloromethane. The organic layer was dried (MgSO₄) and evaporated. The residue (64.3g) was purified by column chromatography over silica gel (eluent : CH₂Cl₂/CH₃OH/NH₄OH 96/4/0.1 to 90/10/0.1) (35-70μm). The pure fractions were collected and evaporated, yielding 29.55g (41%) of (1-methyl-4-piperidinyl)[2-[2-(3-thienyl)ethyl]-2H-1,2,4-triazol-3-yl]methanone (interm. 3);

In a similar way there were prepared :

(1-methyl-4-piperidinyl)[1-[2-(1-methyl-1H-pyrrol-2-yl)ethyl]-1H-1,2,4-triazol-5-yl]methanone (interm. 4);

[1-[2-(4-methoxyphenyl)ethyl]-4-piperidinyl][2-[2-(1-methyl-1H-pyrrol-2-yl)ethyl]-2H-1,2,4-triazol-3-yl]methanone (interm. 5);

[1-[2-(4-methoxyphenyl)ethyl]-4-piperidinyl][2-[2-(3-thienyl)ethyl]-2H-1,2,4-triazol-3-yl]methanone (interm. 28); and

[2-[2-(5-methyl-2-furanyl)ethyl]-2H-1,2,4-triazol-3-yl](1-methyl-4-piperidinyl)-methanone (interm. 29).

c) Tin(IV)chloride (0.394 mol) was added dropwise at room temperature to a solution of intermediate (3) (0.0985 mol) in 1,2-dichloroethane (500ml) and the mixture was stirred and heated at 80°C for 4 hours. The mixture was cooled, poured into ice, basified with ammonia and extracted with dichloromethane. The organic layer was washed with water, dried (MgSO₄), filtered off and evaporated till dryness. The residue was purified by column chromatography over silica gel (eluent : CH₂Cl₂/CH₃OH/NH₄OH 92/8/1 then 85/15/1). The pure fractions were collected and evaporated, yielding 16.4g (55%) of product. A sample (3.2g) was dissolved in methanol and the mixture was refluxed for several hours in the presence of norit. The mixture was filtered over celite and the filtrate was evaporated in vacuo. The residue was crystallized from 2-propanone/1,1'-oxybisethane, yielding 1.44g of (±)-6,10-dihydro-10-(1-methyl-4-piperidiny)-5H-thieno[2,3-d][1,2,4]triazolo[1,5-a]azepin-10-ol; mp. 158.3°C (interm. 6).

In a similar way there was prepared :

(±)-6,10-dihydro-10-[1-[2-(4-methoxyphenyl)ethyl]-4-piperidiny]-5H-thieno[2,3-d][1,2,4]triazolo[1,5-a]azepin-10-ol (interm. 30).

Example 2

[0074]

a) Hydrazine monohydrate (65ml) was added dropwise to a solution of methyl 1-methyl-1H-pyrrole-2-acetate (0.326 mol) in ethanol (300ml) and the mixture was refluxed for 4 hours. The mixture was evaporated till dryness. The residue was taken up in dichloromethane and an aqueous potassium carbonate solution (10%) and extracted with dichloromethane. The organic layer was dried (MgSO₄) and evaporated. The residue (48.8g) was taken up in 1,1'-oxybisethane and the precipitate was filtered off, yielding 45.3g (90%) of 1-methyl-1H-pyrrole-2-acetic acid, hydrazine (interm. 7).

b) 2-isothiocyanato-1,1-dimethoxyethane (0.357 mol) was added dropwise to a solution of intermediate (7) (0.286 mol) in benzene (500ml) and the mixture was stirred and refluxed for 1 hour. The mixture was cooled to 0°C. The precipitate was filtered off and dried with 1,1'-oxybisethane, yielding 78.2g (91%) of 2-[[2,2-dimethoxyethyl]amino]thioxymethyl]-1-methyl-1H-pyrrole-2-acetic acid, hydrazide (interm. 8).

c) A mixture of intermediate (8) (0.26 mol) in potassium hydroxide 2N (524ml) was refluxed for 2 hours. The mixture was cooled on an ice bath. Ammonium chloride was added and filtered off. The precipitate was washed with water and dried in vacuo, yielding 61.72g (84%) of 4-(2,2-dimethoxyethyl)-5-[(1-methyl-1H-pyrrol-2-yl)methyl]-4H-1,2,4-triazole-3-thiol (interm. 9).

d) Iodomethane (15.4ml) was added to a solution of intermediate (9) (0.193 mol) in a solution of sodium methoxide in methanol (53.2ml) and methanol (500ml) and the mixture was stirred at room temperature for 2 hours. The mixture was evaporated, the residue was taken up in water and extracted with dichloromethane. The organic layer was washed with water, dried (MgSO₄) and evaporated. The residue was taken up in 1,1'-oxybisethane and the precipitate was filtered off, yielding 56g (98%) of 4-(2,2-dimethoxyethyl)-3-[(1-methyl-1H-pyrrol-2-yl)methyl]-5-(methylthio)-4H-1,2,4-triazole (interm. 10).

e) A mixture of intermediate (10) (0.287 mol) in sulfuric acid (500ml) was stirred at 0°C for 2 hours. The mixture was poured into ice water, alkalinized with ammonia and extracted with dichloromethane (+ methanol). The organic layer was dried (MgSO₄) and evaporated. The residue (39.67g) was purified by column chromatography over silica gel (eluent : CH₂Cl₂/CH₃OH/NH₄OH 98/2/0.1 to 97/3/0.1) (35-70μm). The pure fractions were collected and evaporated, yielding 25g (34%) of 9,10-dihydro-9-methyl-3-(methylthio)pyrrolo[2,3-d]-1,2,4-triazolo[4,3-a]azepine (interm. 11).

f) Intermediate (11) (0.108 mol) was refluxed with Raney nickel catalyst (140g) (washed with methanol) in ethanol (400ml) for 24 hours. The mixture was heated for 24 hours more. The catalyst was filtered off and the solvent was evaporated. The residue (15g) was purified by column chromatography over silica gel (eluent : CH₂Cl₂/CH₃OH/NH₄OH 98/2/0.1). The pure fractions were collected and evaporated, yielding 10.6g (53%) of product. A sample (2g) was recrystallized from methanol/1,1'-oxybisethane, yielding 1.5g of 9,10-dihydro-9-methylpyrrolo[2,3-d]-1,2,4-triazolo[4,3-a]azepine; mp. 177.7°C (interm. 12).

Example 3

[0075]

a) A mixture of O-ethyl 3-thiopheneethanimidate hydrochloride (0.14 mol) in 1,2-dimethoxyethane (150ml) was stirred at 15°C. 2,2-dimethoxyethanamine (0.14 mol) was added portionwise and the mixture was stirred overnight. The mixture was evaporated, yielding N-(2,2-dimethoxyethyl)-3-thiopheneethanimidamide monohydrochloride

(interm. 13).

In a similar way, but in tetrahydrofuran as a solvent, was prepared :

N-(2,2-dimethoxyethyl)-2-thiopheneethanimidamide monohydrochloride (interm. 14).

b) A mixture of intermediate (13) (0.14 mol) in acetic acid (150ml) was stirred under nitrogen. Methanesulfonic acid (27g) was added portionwise and the mixture was stirred overnight. The mixture was poured into ice and alkalinized with sodium hydroxide. The precipitate was filtered off and the water layer was extracted with dichloromethane / methanol and evaporated. The precipitate and the residue were put together, yielding 13.8g (60%) of 4H-thieno[2,3-d]azepin-5-amine (interm. 15). In a similar way, but using hydrogen bromide 30% in acetic acid instead of methanesulfonic acid, was prepared :

8H-thieno[2,3-d]azepin-7-amine (interm. 16).

c) A mixture of intermediate (15) (0.153 mol) in hydrazine monohydrate (31.35ml) and methanol (780ml) was stirred at room temperature for 30 minutes. The mixture was evaporated in vacuo at 40°C till a volume of 200ml, diluted in water and filtered off, yielding fraction 1. The aqueous layer was extracted with dichloromethane. The organic layer was washed with water, dried (MgSO₄), filtered off and evaporated, yielding fraction 2. The 2 fractions were put together, yielding 19.88g (73%) of 5-hydrazino-4H-thieno[2,3-d]azepine (interm. 17).

In a similar way there was prepared :

7-hydrazino-8H-thieno[2,3-d]azepine (interm. 18).

d) A mixture of intermediate (17) (0.111 mol) and methanimidamide acetate (0.166 mol) in ethanol (1200ml) was refluxed for 2 hours 30 minutes. The cooled solution was filtered off and evaporated in vacuo. The residue was dissolved in dichloromethane, washed with water, dried (MgSO₄), filtered off and evaporated. The residue was crystallized from 2,2'-oxybispropane, yielding 15.58g (74%) of product. A sample was purified by column chromatography over silica gel (eluent : CH₂Cl₂/CH₃OH 97/3). The pure fractions were collected and evaporated. The residue was recrystallized from ethyl acetate/2,2'-oxybispropane, yielding 1.08g of 10H-thieno[3,2-d]-1,2,4-triazolo[4,3-a]azepine; mp. 146.3°C (interm. 19).

In a similar way there was prepared :

10H-thieno[2,3-d]-1,2,4-triazolo[4,3-a]azepine; mp. 184.1°C (interm. 20).

e) A mixture of intermediate (19) (0.0835 mol) and manganese dioxide (158g) in N,N-dimethylformamide (840ml) was stirred rapidly and heated at 40°C for 48 hours. The mixture was filtered hot over celite, washed with hot N,N-dimethylformamide and evaporated in vacuo. The residue was taken up in 2-propanone/2,2'-oxybispropane and filtered off. The precipitate was washed with 2,2'-oxybispropane and dried, yielding 9.85g (58%) of 10H-thieno[3,2-d]-1,2,4-triazolo[1,5-a]azepin-10-one (interm. 21).

In a similar way there was prepared :

9-methylpyrrolo[2,3-d]-1,2,4-triazolo[4,3-a]azepin-10(9H)-one (interm. 22).

In a similar way, but in a mixture of acetic acid and water as a solvent, was prepared : 10H-thieno[2,3-d][1,2,4]triazolo[4,3-a]azepin-10-one (interm. 23).

f) 1,2-dibromoethane (few drops) was added to a stirring mixture of magnesium turnings (0.105 mol) in tetrahydrofuran (5ml) under nitrogen. When the reaction was started, pure 4-chloro-1-methylpiperidine (few drops) was added, the remaining 4-chloro-1-methylpiperidine (0.115 mol) in tetrahydrofuran (50ml) was added dropwise to maintain a temperature between 40 and 50°C. The mixture was diluted with tetrahydrofuran (50ml) and refluxed for 2 hours. A suspension of intermediate (21) (0.049 mol) in tetrahydrofuran (200ml) was added portionwise at 60°C and the mixture was refluxed for 2 hours. The mixture was cooled, decomposed with an ammonium chloride solution and extracted with dichloromethane / methanol. The organic layer was dried (MgSO₄), filtered off and evaporated. The residue was purified by column chromatography over silica gel (eluent 1 : CH₂Cl₂/CH₃OH/NH₄OH 90/10/1 and eluent 2 : CH₂Cl₂/CH₃OH/NH₄OH 50/50/1). The pure fractions were collected and evaporated, yielding 2.53g (17%) of 10-(1-methyl-4-piperidinyl)-10H-thieno[3,2-d]-1,2,4-triazolo[1,5-a]azepin-10-ol (interm. 24).

In a similar way there were prepared :

(±)-9,10-dihydro-9-methyl-10-(1-methyl-4-piperidinyl)pyrrolo[2,3-d]-1,2,4-triazolo[4,3-a]azepin-10-ol (interm. 25); and

(±)-10-(1-methyl-4-piperidinyl)-10H-thieno[2,3-d][1,2,4]triazolo[4,3-a]azepin-10-ol (interm. 26).

B. Preparation of the final compounds

Example 4

[0076] A mixture of intermediate (25) (0.008 mol) in phosphorus oxychloride (96ml) was stirred and refluxed for 2 hours. The mixture was cooled and evaporated in vacuo. The residue was taken up in water, basified with ammonia, extracted with dichloromethane and washed with water. The organic layer was dried (MgSO₄), filtered off and evaporated. The residue (2g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH/NH₄OH

94.5/5/0.5). The pure fractions were collected and evaporated. The residue (1.5g) was recrystallized from 2-butanone / methanol, yielding 0.8g (36%) of 9,10-dihydro-9-methyl-10-(1-methyl-4-piperidinylidene)pyrrolo[2,3-d]-1,2,4-triazolo[4,3-a]azepine; mp. 262.0°C (comp. 1).

In a similar way there were prepared :

- 5 10-(1-methyl-4-piperidinylidene)-10H-thieno[3,2-d]-1,2,4-triazolo[4,3-a]azepine; mp. 244.9°C (comp. 2);
 10-(1-methyl-4-piperidinylidene)-10H-thieno[2,3-d][1,2,4]triazolo[4,3-a]azepine; mp. 239.5°C (comp. 3);
 6,10-dihydro-10-[1-[2-(4-methoxyphenyl)ethyl]-4-piperidinylidene]-5H-thieno[2,3-d][1,2,4]triazolo[1,5-a]azepine ethan-
 edioate(2:3) monohydrate; mp. 158.6°C (comp. 16); and
 10 (±)-10-[1-[2-(4-methoxyphenyl)ethyl]-4-piperidinyl]-10H-thieno[2,3-d][1,2,4] triazolo [1,5-a]azepine; mp. 170.8°C
 (comp. 17).

Example 5

- 15 **[0077]** Intermediate (4) (0.116 mol) was added portionwise to methanesulfonic acid (210ml) at 0°C and the mixture was stirred at 80°C for 3 hours. The mixture was poured into ice, basified with sodium hydroxide and extracted with dichloromethane. The organic layer was dried (MgSO₄) and evaporated till dryness. The residue (28g) was purified by column chromatography over silica gel (eluent : CH₂Cl₂/CH₃OH/NH₄OH 95/5/0.2) (15μm). The pure fractions were collected and evaporated. The residue (0.87g) was crystallized from 1,1'-oxybisethane, yielding 0.67g (2%) of 5,6,7,10-tetrahydro-7-methyl-10-(1-methyl-4-piperidinylidene)pyrrolo[3,2-d][1,2,4]triazolo[1,5-a]azepine; mp. 169.1°C (comp. 4).

Example 6

- 25 **[0078]** Tin(IV)chloride (12.6ml) was added dropwise at room temperature to a solution of intermediate (5) (0.0285 mol) in 1,2-dichloroethane (300ml) and the mixture was stirred and heated at 80°C for 2 hours. The mixture was cooled, poured into ice and basified with ammonia. The mixture was filtered over celite and the filtrate was extracted with dichloromethane. The organic layer was dried (MgSO₄) and evaporated. The residue (11.52g) was purified by column chromatography over silica gel (eluent : CH₂Cl₂/CH₃OH/NH₄OH 97/3/0.1 to 95/5/0.1) (35-70μm). The pure fractions were collected and evaporated. The residue (4.4g) was recrystallized from 2-butanone and 2,2'-oxybispropane, yielding 3.19g (38%) of (±)-7,10-dihydro-10-[1-[2-(4-methoxyphenyl)ethyl]-4-piperidinyl]-7-methylpyrrolo[3,2-d]-1,2,4-triazolo[1,5-a]azepine; mp. 140.1°C (comp. 5).

In a similar way there was prepared :

(±)-8-methyl-10-(1-methyl-4-piperidinyl)-10H-furo[3,2-d][1,2,4]triazolo[1,5-a]azepine; mp. 111.8°C (comp. 18).

Example 7

- 35 **[0079]** Compound (1) (0.00355 mol) in ethanol (250ml) was hydrogenated with palladium on activated carbon 10% (1g) as a catalyst for 6 hours at room temperature under a 3 bar pressure in a Parr apparatus. After uptake of hydrogen (1eq.), the catalyst was filtered through celite and the filtrate was evaporated. The residue (0.9g) was purified by column chromatography over silica gel (eluent : CH₂Cl₂/CH₃OH/ NH₄OH 95/5/0.5) (15-40μm). The pure fractions were collected and evaporated. The residue (0.7g) was crystallized from 2-butanone/2,2'-oxybispropane, yielding 0.57g (70%) of 5,6,9,10-tetrahydro-9-methyl-10-(1-methyl-4-piperidinylidene)pyrrolo[2,3-d]-1,2,4-triazolo[4,3-a]azepine; mp. 214.1°C (comp. 6);

In a similar way there were prepared :

- 45 (±)-5,6,7,10-tetrahydro-10-[1-[2-(4-methoxyphenyl)ethyl]-4-piperidinyl]-7-methylpyrrolo[3,2-d]-1,2,4-triazolo[1,5-a]azepine; 132.1°C (comp. 7); and (±)-5,6,7,10-tetrahydro-7-methyl-10-(1-methyl-4-piperidinyl)pyrrolo[3,2-d][1,2,4]triazolo[1,5-a]azepine; mp. 142.8°C (comp. 8).

Example 8

- 50 **[0080]**

a) A mixture of intermediate (6) (0.034 mol) in phosphoric acid 98% (80ml) was stirred and heated at 100°C for 6 hours. The mixture was cooled, poured into ice water, basified with ammonia and extracted with dichloromethane. The organic layer was dried (MgSO₄) and evaporated. The residue (10.61g) was purified by column chromatography over silica gel (eluent : CH₂Cl₂/CH₃OH/NH₄OH 95/5/0.1 to 90/10/0.1 to 75/25/0.2) (35-70μm). The pure fractions were collected and evaporated. Fraction 1 was crystallized from n-pentane, yielding 1.6g (21%) of 6,10-dihydro-10-(1-methyl-4-piperidinylidene)-5H-thieno[2,3-d][1,2,4]triazolo[1,5-a]azepine; 141.2°C (comp. 9). Fraction 2 was treated with norit in methanol and crystallized from n-pentane, yielding 1.12g (12%) of (±)-10-(1-methyl-4-

piperidiny]-10H-thieno[2,3-d][1,2,4]triazolo[1,5-a]azepine; mp. 136.7°C (comp. 10).

b) A mixture of compound (10) (0.00342 mol) and compound (9) (0.00342 mol) was hydrogenated in acetic acid (1.65ml) and ethanol (150ml) with palladium on activated carbon (2g) as a catalyst at 50°C overnight under a 3 bar pressure in a Parr apparatus. The catalyst was filtered through celite and the filtrate was evaporated till dryness. The residue was taken up in dichloromethane and washed with potassium carbonate 10%. The organic layer was dried (MgSO₄), filtered off and evaporated. The residue was purified by column chromatography over silica gel (eluent : CH₂Cl₂/CH₃OH/NH₄OH 90/10/1) (15-40μm). The pure fractions were collected and evaporated. The residue (1.5g) was crystallized from 2,2'-oxybispropane, yielding 0.92g (76%) of (±)-6,10-dihydro-10-(1-methyl-4-piperidiny]-5H-thieno[2,3-d][1,2,4]triazolo[1,5-a]azepine; mp. 123.4°C (comp. 11).

Example 9

[0081]

a) Carbonochloridic acid ethyl ester (14.8ml) was added dropwise at 80°C to a solution of compound (4) (0.0193 mol) in N,N-diethylethanamine (5.4ml) and methylbenzene (500ml) and the mixture was stirred and refluxed for 3 hours. The mixture was cooled, poured into water, decanted off and extracted with ethyl acetate. The organic layer was washed with water, dried (MgSO₄), filtered off and evaporated. The residue (9.34g) was purified by column chromatography over silica gel (eluent : CH₂Cl₂/CH₃OH/NH₄OH 97.5/2.5/0.1) (15μm). The pure fractions were collected and evaporated. The residue was recrystallized from 2-butanone/2,2'-oxybispropane yielding 1.8g (36%) of ethyl 4-(5,6,7,10-tetrahydro-7-methylpyrrolo[3,2-d][1,2,4]triazolo[1,5-a]azepin-10-ylidene)-1-piperidinecarboxylate monohydrate; mp. 104.1°C (comp. 12).

In a similar way there was prepared :

ethyl 4-(5, 6-dihydro-10H-thieno[2,3-d][1,2,4]triazolo[1,5-a]azepin-10-ylidene)-1-piperidinecarboxylate (comp. 13);

(±)-ethyl 4-(10H-thieno[2,3-d][1,2,4]triazolo[1,5-a]azepin-10-yl)-1-piperidinecarboxylate (comp. 19); and

ethyl 10-(10H-thieno[3,2-d]-1,2,4-triazolo[4,3-a]azepin-10-ylidene)-1-piperidinecarboxylate (comp. 20).

b) Compound (12) (0.0205 mol) was heated in a solution of potassium hydroxide (11.5g) in 2-propanol (175ml) and water (175ml) for 63 hours. The mixture was cooled and evaporated. The residue was diluted in water (200ml) and extracted with dichloromethane. The organic layer was dried (MgSO₄), filtered off and evaporated. The residue (5.95g) was purified by column chromatography over silica gel (eluent : CH₂Cl₂/CH₃OH/NH₄OH 92/8/0.5 to 80/20/0.5). The pure fractions were collected and evaporated, yielding 4.1g (74%) of product. A sample (2g) was crystallized from 2-butanone/2,2'-oxybispropane, yielding 1.8g of 5,6,7,10-tetrahydro-7-methyl-10-(4-piperidinyldene)pyrrolo[3,2-d][1,2,4]triazolo[1,5-a]azepine; mp. 183.1°C (comp. 14).

In a similar way, but in an acid environment, was prepared :

6,10-dihydro-10-(4-piperidinyldene)-5H-thieno[2,3-d][1,2,4]triazolo[1,5-a]azepine; 198.8°C (comp. 15);

(±)-10-(4-piperidiny]-10H-thieno[2,3-d][1,2,4]triazolo[1,5-a]azepine hemihydrate; mp. 136.3°C (comp. 21); and

10-(4-piperidinyldene)-10H-thieno[3,2-d]-1,2,4-triazolo[4,3-a]azepine (comp. 22).

Example 10

[0082] A mixture of compound (14) (0.00471 mol), 1-(2-bromoethyl)-4-methoxybenzene (0.007 mol), potassium iodide (0.08g) and potassium carbonate (1.3g) in 4-methyl-2-pentanone (50ml) was stirred and refluxed overnight. The mixture was cooled and evaporated. The residue was taken up in dichloromethane. The organic layer was washed with water, dried (MgSO₄), filtered off and evaporated. The residue (4g) was purified by column chromatography over silica gel (eluent : CH₂Cl₂/CH₃OH/NH₄OH 97/3/0.2) (15μm). The pure fractions were collected and evaporated. The residue (1.45g) was recrystallized from ethanol/2,2'-oxybispropane, yielding 1.14g (55%) 5,6,7,10-tetrahydro-10-[1-[2-(4-methoxyphenyl)ethyl]-4-piperidinyldene]-7-methylpyrrolo[3,2-d][1,2,4]triazolo[1,5-a]azepine; mp. 138.9°C (comp. 23).

In a similar way there were prepared :

10-[1-[3-(4-fluorophenoxy)propyl]-4-piperidinyldene]-6,10-dihydro-5H-thieno[2,3-d][1,2,4]triazolo[1,5-a]azepine; mp. 131.3°C (comp. 24);

(±)-(E)-10-[1-(3-phenyl-2-propenyl)-4-piperidiny]-10H-thieno[2,3-d][1,2,4]triazolo[1,5-a]azepine; mp. 149.0°C (comp. 25);

1-ethyl-1,4-dihydro-4-[2-[4-(5,6,7,10-tetrahydro-7-methylpyrrolo[3,2-d][1,2,4]triazolo[1,5-a]azepin-10-ylidene)-1-piperidiny]ethyl]-5H-tetrazol-5-one (comp. 26);

10-[1-(2-ethoxyethyl)-4-piperidinyldene]-6,10-dihydro-5H-thieno[2,3-d][1,2,4]triazolo[1,5-a]azepine; mp. 82.5°C (comp. 27); and

(±)-2-methyl-3-[2-[4-(10H-thieno[2,3-d][1,2,4]triazolo[1,5-a]azepin-10-yl)-1-piperidiny]ethyl]-4H-pyrido[1,2-a]pyrimidin-

4-one; mp. 200.1°C (comp. 28).

Example 11

[0083] A mixture of compound (14) (0.0092 mol) and methyl 2-propenoate (0.018 mol) in methanol (40ml) was stirred and refluxed overnight. The mixture was evaporated till dryness. The residue (2.7g) was purified by column chromatography over silica gel (eluent : CH₂Cl₂/CH₃OH/NH₄OH 96/4/0.2). The pure fractions were collected and evaporated. The residue was crystallized from 2-propanone/2,2'-oxybispropane, yielding 1.3g (52%) of methyl 4-(5,6,7,10-tetrahydro-7-methylpyrrolo[3,2-d][1,2,4]triazolo[1,5-a]azepin-10-ylidene)-1-piperidinepropanoate; mp. 138.9°C (comp. 29).

In a similar way there was prepared :

methyl 10-(10H-thieno[3,2-d]-1,2,4-triazolo[4,3-a]azepin-10-ylidene)-1-piperidinepropanoate; mp. 128.1°C (comp. 30).

Example 12

[0084] Oxirane (0.017 mol) was bubbled through methanol at 0°C. This mixture was added dropwise over a 30 minutes period to a solution of compound (15) (0.00844 mol) in methanol at room temperature. The mixture was stirred at room temperature for 24 hours. The mixture was evaporated and the residue was taken up in dichloromethane. The organic layer was washed with water, dried (MgSO₄), filtered off and evaporated. The residue was purified by column chromatography over silica gel (eluent : CH₂Cl₂/CH₃OH/NH₄OH 95/5/0.5) (15-40μm). The pure fractions were collected and evaporated. The residue (2g) was recrystallized from 2-propanone, yielding 1.15g (43%) of 4-(5,6-dihydro-10H-thieno[2,3-d][1,2,4]triazolo[1,5-a]azepin-10-ylidene)-1-piperidineethanol; mp. 149.8°C (comp. 31).

Example 13

[0085]

a) At 0 °C, phosphoryl chloride (0.022 mol) was added dropwise to N,N-dimethylformamide (13 ml). This mixture was stirred for 30 minutes. Compound (4) (0.0106 mol) was added portionwise at 0 °C. Then, the temperature was raised to 30 °C and stirring at this temperature was continued for 3 hours. The reaction mixture was cooled, poured out into ice water and the resulting solution was alkalized with potassium carbonate. This mixture was extracted with dichloromethane. The separated organic layer was washed with water, dried (MgSO₄), filtered, treated with activated charcoal, filtered over diatomaceous earth and the filtrate was evaporated. The residue was crystallized from 2,2'-oxybispropane. The precipitate was filtered off (2.2 g) and recrystallized from acetonitrile. The precipitate was filtered off and dried, yielding 1.3g (39%) of 5,6,7,10-tetrahydro-7-methyl-10-(1-methyl-4-piperidinylidene)pyrrolo[3,2-d][1,2,4]triazolo[1,5-a]azepine-8-carboxaldehyde; mp. 204.5°C (comp. 32).

b) A mixture of compound (32) (0.018 mol) in methanol (190ml) was cooled till 0°C. Sodium borohydride (5.8g) was added portionwise and the mixture was stirred for 1 hour. The mixture was poured into ice and extracted with dichloromethane. The organic layer was washed with water, dried (MgSO₄), filtered off and evaporated till dryness. The residue (5.05g) was purified by column chromatography over silica gel (eluent : CH₂Cl₂/CH₃OH/NH₄OH 92/8/0.5). The pure fractions were collected and evaporated. The product was recrystallized from 2,2'-oxybispropane, yielding 1.4g (24%) of 5,6,7,10-tetrahydro-7-methyl-10-(1-methyl-4-piperidinylidene)pyrrolo[3,2-d][1,2,4]triazolo[1,5-a]azepine-8-methanol hemihydrate; mp. 201.2°C (comp. 33).

C. Composition Examples

[0086] The following formulations exemplify typical pharmaceutical compositions in dosage unit form suitable for systemic or topical administration to warm-blooded animals in accordance with the present invention.

"Active ingredient" (A.I.) as used throughout these examples relates to a compound of formula (I) or a compound of formula (VII), a pharmaceutically acceptable acid addition salt or a stereochemically isomeric form thereof.

Example 14 : Oral drops

[0087] 500 g of the A.I. is dissolved in 0.5 l of 2-hydroxypropanoic acid and 1.5 l of the polyethylene glycol at 60~80°C. After cooling to 30~40°C there are added 35 l of polyethylene glycol and the mixture is stirred well. Then there is added a solution of 1750 g of sodium saccharin in 2.5 l of purified water and while stirring there are added 2.5 l of cocoa flavor and polyethylene glycol q.s. to a volume of 50 l, providing an oral drop solution comprising 10 mg/ml of the A.I. The resulting solution is filled into suitable containers.

Example 15 : Oral solutions

[0088] 9 g of methyl 4-hydroxybenzoate and 1 g of propyl 4-hydroxybenzoate are dissolved in 4 l of boiling purified water. In 3 l of this solution are dissolved first 10 g of 2,3-dihydroxybutanedioic acid and thereafter 20 g of the A.I. The latter solution is combined with the remaining part of the former solution and 12 l of 1,2,3-propanetriol and 3 l of sorbitol 70% solution are added thereto. 40 g of sodium saccharin are dissolved in 0.5 l of water and 2 ml of raspberry and 2 ml of gooseberry essence are added. The latter solution is combined with the former, water is added q.s. to a volume of 20 l providing an oral solution comprising 5 mg of the A.I. per teaspoonful (5 ml). The resulting solution is filled in suitable containers.

Example 16 : Capsules

[0089] 20 g of the A.I., 6 g sodium lauryl sulfate, 56 g starch, 56 g lactose, 0.8 g colloidal silicon dioxide, and 1.2 g magnesium stearate are vigorously stirred together. The resulting mixture is subsequently filled into 1000 suitable hardened gelatin capsules, each comprising 20 mg of the A.I.

Example 17 : Film-coated tabletsPreparation of tablet core

[0090] A mixture of 100 g of the A.I., 570 g lactose and 200 g starch is mixed well and thereafter humidified with a solution of 5 g sodium dodecyl sulfate and 10 g polyvinylpyrrolidone (Kollidon-K 90®) in about 200 ml of water. The wet powder mixture is sieved, dried and sieved again. Then there are added 100 g microcrystalline cellulose (Avicel®) and 15 g hydrogenated vegetable oil (Sterotex®). The whole is mixed well and compressed into tablets, giving 10.000 tablets, each comprising 10 mg of the active ingredient.

Coating

[0091] To a solution of 10 g methyl cellulose (Methocel 60 HG®) in 75 ml of denaturated ethanol there is added a solution of 5 g of ethyl cellulose (Ethocel 22 cps®) in 150 ml of dichloromethane. Then there are added 75 ml of dichloromethane and 2.5 ml 1,2,3-propanetriol. 10 g of polyethylene glycol is molten and dissolved in 75 ml of dichloromethane. The latter solution is added to the former and then there are added 2.5 g of magnesium octadecanoate, 5 g of polyvinylpyrrolidone and 30 ml of concentrated colour suspension (Opaspray K-1-2109®) and the whole is homogenated. The tablet cores are coated with the thus obtained mixture in a coating apparatus.

Example 18 : Injectable solutions

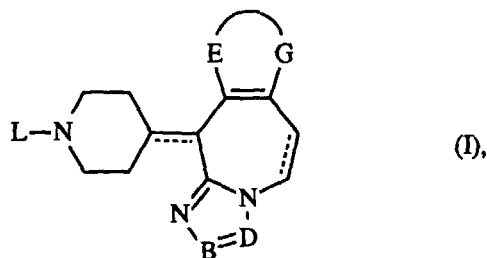
[0092] 1.8 g methyl 4-hydroxybenzoate and 0.2 g propyl 4-hydroxybenzoate are dissolved in about 0.5 l of boiling water for injection. After cooling to about 50°C there are added while stirring 4 g lactic acid, 0.05 g propylene glycol and 4 g of the A.I.. The solution is cooled to room temperature and supplemented with water for injection q.s. ad 1 l volume, giving a solution of 4 mg A.I. per ml. The solution is sterilized by filtration (U.S.P. XVII p. 811) and filled in sterile containers.

Example 19 : Suppositories

[0093] 3 g A.I. is dissolved in a solution of 3 g 2,3-dihydroxybutanedioic acid in 25 ml polyethylene glycol 400. 12 g surfactant (SPAN®) and triglycerides (Witepsol 555®) q.s. ad 300 g are molten together. The latter mixture is mixed well with the former solution. The thus obtained mixture is poured into moulds at a temperature of 37-38°C to form 100 suppositories each containing 30 mg of the A.I.

Claims

1. A compound having the formula



a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof, wherein each of the dotted lines independently represents an optional bond;

15 -E-G- is a bivalent radical of formula



or



X represents O, S or NR³;

R³ represents hydrogen, C₁₋₆alkyl or C₁₋₄alkylcarbonyl;

25 R¹ and R² each independently represent hydrogen, C₁₋₄alkyl, halo, ethenyl substituted with hydroxycarbonyl or C₁₋₄alkyloxycarbonyl, hydroxyC₁₋₄alkyl, formyl, hydroxycarbonyl or hydroxycarbonylC₁₋₄alkyl;

-B=D- is a bivalent radical of formula



or



35 R⁴ represents hydrogen or C₁₋₄alkyl;

R⁵ represents hydrogen or C₁₋₄alkyl;

L represents hydrogen; C₁₋₆alkyl; C₁₋₆alkyl substituted with one substituent selected from the group consisting of hydroxy, C₁₋₄alkyloxy, hydroxycarbonyl, C₁₋₄alkyloxycarbonyl, C₁₋₄alkyloxycarbonylC₁₋₄alkyloxy, hydroxycarbonylC₁₋₄alkyloxy, C₁₋₄alkylaminocarbonylamino, C₁₋₄alkylaminothiocarbonylamino, aryl and aryloxy; C₁₋₆alkyl substituted with both hydroxy and aryloxy; C₃₋₆alkenyl; C₃₋₆alkenyl substituted with aryl; wherein each aryl is phenyl or phenyl substituted with halo, cyano, hydroxy, C₁₋₄alkyl, C₁₋₄alkyloxy or aminocarbonyl; or,

L represents a radical of formula



or



wherein

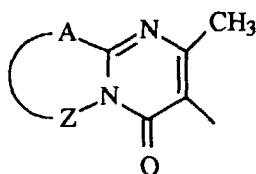
Alk represents C₁₋₄alkanediyl ;

55 Y represents O, S or NH ;

Het¹, Het² and Het³ each represent furanyl, thienyl, oxazolyl, thiazolyl or imidazolyl each optionally substituted with one or two C₁₋₄alkyl substituents; pyrrolyl or pyrazolyl optionally substituted with formyl, hydroxyC₁₋₄alkyl, hydroxycarbonyl, C₁₋₄alkyloxycarbonyl or with one or two C₁₋₄alkyl substit-

uents; thiadiazolyl or oxadiazolyl optionally substituted with amino or C₁₋₄alkyl; pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl each optionally substituted with C₁₋₄alkyl, C₁₋₄alkyloxy, amino, hydroxy or halo; and

Het³ may also represent 4,5-dihydro-5-oxo-1H-tetrazolyl substituted with C₁₋₄alkyl, 2-oxo-3-oxazolidinyl, 2,3-dihydro-2-oxo-1H-benzimidazol-1-yl or a radical of formula



wherein

A-Z represents S-CH=CH, S-CH₂-CH₂, S-CH₂-CH₂-CH₂, CH=CH-CH=CH, or CH₂-CH₂-CH₂-CH₂.

2. A compound according to claim 1 wherein R¹, R², R⁴ and R⁵ are hydrogen.

3. A compound according to claim 2 wherein X is S or NCH₃.

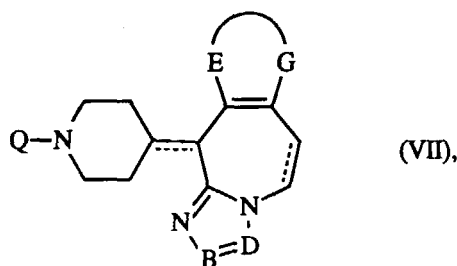
4. A compound according to claim 1 wherein said compound is selected from the group consisting of 5,6,7,10-tetrahydro-7-methyl-10-(1-methyl-4-piperidinylidene)pyrrolo[3,2-d][1,2,4]triazolo[1,5-a]azepine; 10-(1-methyl-4-piperidinylidene)-10H-thieno[3,2-d]-1,2,4-triazolo[4,3-a]azepine; and 6,10-dihydro-10-(1-methyl-4-piperidinylidene)-5H-thieno[2,3-d][1,2,4]triazolo[1,5-a]azepine, the stereoisomers and the pharmaceutically acceptable acid-addition salts thereof.

5. A pharmaceutical composition comprising as an active ingredient a therapeutically effective amount of a compound as defined in claim 1 and a pharmaceutically acceptable carrier.

6. A process for preparing a pharmaceutical composition as claimed in claim 5, characterized in that a therapeutically effective amount of a compound as claimed in claim 1 is intimately mixed with a pharmaceutical carrier.

7. A compound as claimed in claim 1 for use as a medicine.

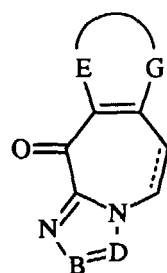
8. A compound having the formula



an addition salt or a stereochemically isomeric form thereof, wherein each of the dotted lines, -E-G- and -B=D- are as defined in claim 1;

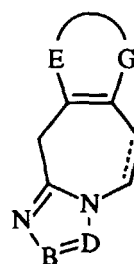
Q represents C₁₋₆alkyloxycarbonyl, C₁₋₄alkylcarbonyl or C₁₋₆alkyl substituted with halo, cyano, amino, or methylsulfonyloxy.

9. A compound having the formula



(XIII)

or



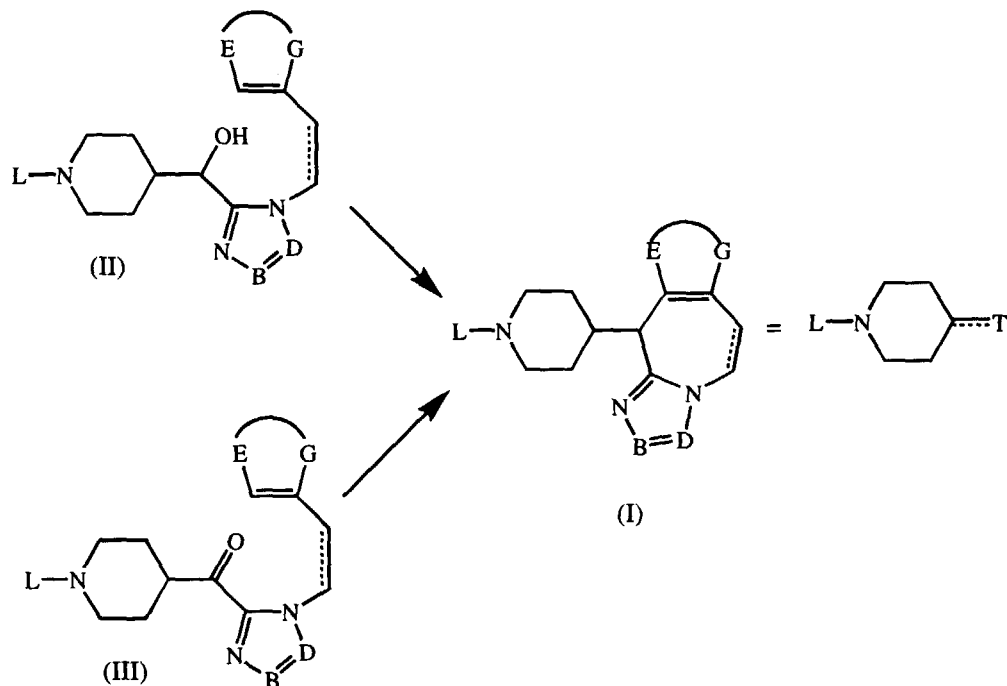
(XIV)

an addition salt or a stereochemically isomeric form thereof, wherein the dotted line, -E-G- and -B=D- are as defined in claim 1.

10. A process for preparing a compound as claimed in claim 1

characterized by

cyclizing an alcohol of formula (II) or a ketone of formula (III) in the presence of an acid;

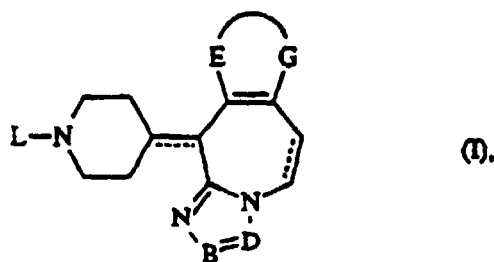


wherein each of the dotted lines independently represents an optional bond, and L, -E-G- and -B=D- are as defined in claim 1;

and further if desired, converting the compounds of formula (I) into each other following art-known functional group transformation procedures; converting the compounds of formula (I) into a salt form by treatment with a pharmaceutically acceptable acid or base; or conversely, converting the salt form into the free base of the free acid by treatment with alkali, respectively an acid; and/or preparing stereochemically isomeric forms thereof.

Patentansprüche

1. Verbindung der Formel



oder eines ihrer pharmazeutisch unbedenklichen Additionssalze oder eine ihrer stereochemisch isomeren Formen, wobei

jede der gestrichelten Linien unabhängig für eine fakultative Bindung steht;

15 -E-G- für einen zweiwertigen Rest der Formel



20 oder



steht,

25 X für O, S oder NR³ steht;

R³ für Wasserstoff, C₁₋₆Alkyl oder C₁₋₄Alkylcarbonyl steht;

R¹ und R² jeweils unabhängig voneinander für Wasserstoff, C₁₋₄Alkyl, Halogen, durch Hydroxycarbonyl oder C₁₋₄Alkyloxycarbonyl substituiertes Ethenyl, für HydroxyC₁₋₄alkyl, Formyl, Hydroxycarbonyl oder HydroxycarbonylC₁₋₄alkyl stehen;

30 -B=D- für einen zweiwertigen Rest der Formel



oder



steht;

40 R⁴ für Wasserstoff oder C₁₋₄Alkyl steht;

R⁵ für Wasserstoff oder C₁₋₄Alkyl steht;

L für Wasserstoff; C₁₋₆Alkyl; C₁₋₆Alkyl, welches durch einen Substituenten aus der Gruppe Hydroxyl, C₁₋₄Alkyloxy, Hydroxycarbonyl, C₁₋₄Alkyloxycarbonyl, C₁₋₄AlkyloxycarbonylC₁₋₄Alkyloxy, HydroxycarbonylC₁₋₄Alkyloxy, C₁₋₄Alkylaminocarbonylamino, C₁₋₄Alkylaminothiocarbonylamino, Aryl oder Aryloxy substituiert ist; C₁₋₆Alkyl, welches sowohl durch Hydroxyl als auch durch Aryloxy substituiert ist; C₃₋₆Alkenyl; C₃₋₆Alkenyl, welches durch Aryl substituiert ist, steht; wobei Aryl jeweils für Phenyl oder durch Halogen, Cyano, Hydroxyl, C₁₋₄Alkyl, C₁₋₄Alkyloxy oder Aminocarbonyl substituiertes Phenyl steht; oder

L steht für einen Rest der Formel



oder



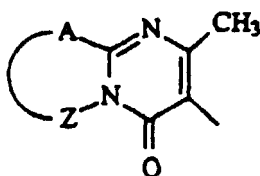
wobei

Alk für C₁₋₄Alkandiy l steht;

Y für O, S oder NH steht;

Het¹, Het² und Het³ jeweils für Furanyl, Thienyl, Oxazolyl, Thiazolyl oder Imidazolyl stehen, die jeweils gegebenenfalls durch einen oder zwei C₁₋₄Alkyl-Substituenten substituiert sind; für Pyrrolyl oder Pyrazolyl stehen, welche gegebenenfalls durch Formyl, HydroxyC₁₋₄Alkyl, Hydroxycarbonyl, C₁₋₄Alkyloxycarbonyl oder durch einen oder zwei C₁₋₄Alkyl-Substituenten substituiert sind; für Thiadiazolyl oder Oxadiazolyl stehen, die gegebenenfalls durch Amino oder C₁₋₄Alkyl substituiert sind; für Pyridinyl, Pyrimidinyl, Pyrazinyl oder Pyridazinyl stehen, die jeweils gegebenenfalls durch C₁₋₄Alkyl, C₁₋₄Alkyloxy, Amino, Hydroxyl oder Halogen substituiert sind; und

Het³ kann auch für 4,5-Dihydro-5-oxo-1H-tetrazolyl stehen, welches durch C₁₋₄Alkyl substituiert ist, für 2-Oxo-3-oxazolidinyl, 2,3-Dihydro-2-oxo-1H-benzimidazol-1-yl oder einen Rest der Formel



stehen, wobei

A-Z für S-CH=CH, S-CH₂-CH₂, S-CH₂-CH₂-CH₂, CH=CH-CH=CH oder CH₂-CH₂-CH₂-CH₂ steht.

2. Verbindung nach Anspruch 1, wobei R¹, R², R⁴ und R⁵ für Wasserstoff stehen.

3. Verbindung nach Anspruch 2, wobei X für S oder NCH₃ steht.

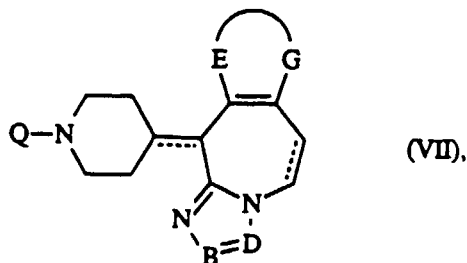
4. Verbindung nach Anspruch 1, wobei die Verbindung unter 5,6,7,10-Tetrahydro-7-methyl-10-(1-methyl-4-piperidinylden)pyrrolo[3,2-d][1,2,4]-triazolo-[1,5-a]-azepin; 10-(1-Methyl-4-piperidinylden)-10H-thieno[3,2-d]-1,2,4-triazolo[4,3-a]azepin; und 6,10-Dihydro-10-(1-methyl-4-piperidinylden)-5H-thieno[2,3-d][1,2,4]triazolo[1,5-a]-azepin, ihren Stereoisomeren und ihren pharmazeutisch unbedenklichen Säureadditionssalzen ausgewählt wird.

5. Pharmazeutische Zusammensetzung, welche als Wirkstoff eine therapeutisch wirksame Menge einer Verbindung nach Anspruch 1 sowie einen pharmazeutisch unbedenklichen Trägerstoff enthält.

6. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung nach Anspruch 5, dadurch gekennzeichnet, daß eine therapeutisch wirksame Menge einer Verbindung nach Anspruch 1 innig mit einem pharmazeutischen Trägerstoff gemischt wird.

7. Verbindung nach Anspruch 1 zur Verwendung als Arzneimittel.

8. Verbindung der Formel

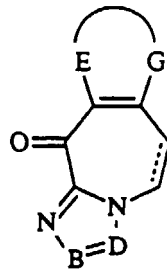


oder eines ihrer Additionssalze oder eine ihrer stereochemisch isomeren Formen, wobei die gestrichelten Linien, -E-G- und -B=D- jeweils wie in Anspruch 1 definiert sind; und

Q für C₁₋₆Alkyloxycarbonyl, C₁₋₄Alkylcarbonyl oder C₁₋₆Alkyl substituiert durch Halogen, Cyano, Amino oder

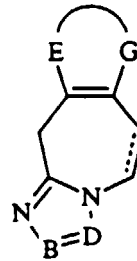
Methylsulfonyloxy, steht.

9. Verbindung der Formel



(XIII)

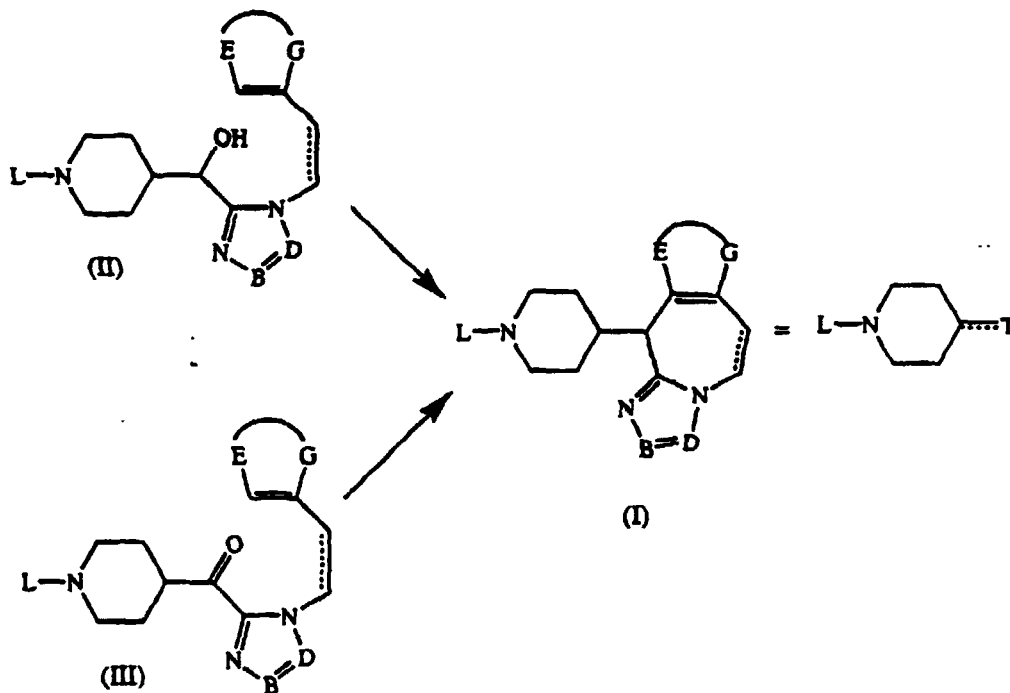
oder



(XIV)

eines ihrer Additionssalze oder eine ihrer stereochemisch isomeren Formen, wobei die gestrichelte Linie, -E-G- und -B=D- wie in Anspruch 1 definiert sind.

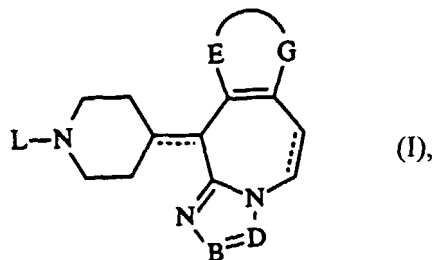
10. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, dadurch gekennzeichnet, daß man einen Alkohol der Formel (II) oder ein Keton der Formel (III) in Gegenwart einer Säure cyclisiert



wobei jede der gestrichelten Linien unabhängig für eine fakultative Bindung steht und L, -E-G- und -B=D- wie in Anspruch 1 definiert sind; und man gewünschtenfalls die Verbindungen der Formel (I) durch dem Fachmann bekannte Umwandlungen funktioneller Gruppen ineinander umwandelt; man die Verbindungen der Formel (I) durch Behandlung mit einer pharmazeutisch unbedenklichen Säure oder Base in eine Salzform überführt; oder umgekehrt die Salzform durch Behandlung mit Alkali bzw. einer Säure in die Freibase der freien Säure umwandelt; und/oder man ihre stereochemisch isomeren Formen herstellt.

Revendications

1. Composé de formule



15 sel d'addition pharmaceutiquement acceptable ou forme stéréochimiquement isomère de celui-ci, dans laquelle chacune des lignes en pointillé représente indépendamment une liaison facultative ;

-E-G- est un radical bivalent de formule



ou



X représente O, S, ou NR^3 ;

R^3 représente un hydrogène, un alkyle en C_{1-6} ou un C_{1-4} -alkylcarbonyle ;

R^1 et R^2 représentent chacun indépendamment un hydrogène, un alkyle en C_{1-4} , un halogéno, un éthényle substitué par un hydroxycarbonyle ou un C_{1-4} -alkyloxycarbonyle, un hydroxy- C_{1-4} -alkyle, un formyle, un hydroxycarbonyle, ou un hydroxycarbonyl- C_{1-4} -alkyle ;

30 -B=D- est un radical bivalent de formule



ou



40 R^4 représente un hydrogène ou un alkyle en C_{1-4} ;

R^5 représente un hydrogène ou un alkyle en C_{1-4} ;

L représente un hydrogène ; un alkyle en C_{1-6} ; un alkyle en C_{1-6} substitué par un substituant choisi parmi le groupe constitué d'un hydroxy, d'un alkyloxy en C_{1-4} , d'un hydroxycarbonyle, d'un C_{1-4} -alkyloxycarbonyle, d'un C_{1-4} -alkyloxycarbonyl- C_{1-4} -alkyloxy, d'un hydroxycarbonyl- C_{1-4} -alkyloxy, d'un C_{1-4} -alkylaminocarbonylamino, d'un C_{1-4} -alkylaminothiocarbonylamino, d'un aryle et d'un aryloxy ; d'un alkyle en C_{1-6} substitué à la fois par un hydroxy et un aryloxy ; un alcényle en C_{3-6} ; un alcényle en C_{3-6} substitué par un aryle ; où chaque aryle est un phényle ou un phényle substitué par un halogéno, un cyano, un hydroxy, un alkyle en C_{1-4} , un alkyloxy en C_{1-4} ou un aminocarbonyle ; ou,

L représente un radical de formule



ou



où

Alk

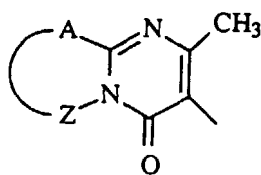
représente un C₁₋₄-alkanediyle ;

Y

représente O, S ou NH ;

Het¹, Het² et Het³

représentent chacun un furanyle, un thiénylène, un oxazolyle, un thiazolyle ou un imidazolyle, chacun éventuellement substitué par un ou deux substituants alkyle en C₁₋₄ ; un pyrrolyle ou un pyrazolyle éventuellement substitué par un formyle, un hydroxy-C₁₋₄-alkyle, un hydroxycarbonylène, un C₁₋₄-alkyloxy-carbonylène, ou par un ou deux substituants alkyle en C₁₋₄ ; un thiadiazolyle ou un oxadiazolyle éventuellement substitué par un amino ou un alkyle en C₁₋₄ ; un pyridinyle, un pyrimidinyle, un pyrazinyle ou un pyridazinyle chacun éventuellement substitué par un alkyle en C₁₋₄, un alkyloxy en C₁₋₄, un amino, un hydroxy, ou un halogéno ; et peut également représenter un 4,5-dihydro-5-oxo-1H-tétrazolyle substitué par un alkyle en C₁₋₄, 2-oxo-3-oxazolidinyle, 2,3-dihydro-2-oxo-1H-benzimidazol-1-yle ou un radical de formule



wherein

A-Z

représente S-CH=CH, S-CH₂-CH₂, S-CH₂-CH₂-CH₂, CH=CH-CH=CH, ou CH₂-CH₂-CH₂-CH₂.

2. Composé selon la revendication 1, dans lequel R¹, R², R⁴ et R⁵ sont un hydrogène.

3. Composé selon la revendication 2, dans lequel X est S ou NCH₃.

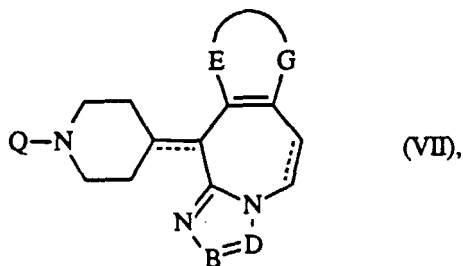
4. Composé selon la revendication 1, ledit composé étant choisi parmi le groupe constitué de 5,6,7,10-tétrahydro-7-méthyl-10-(1-méthyl-4-pipéridinylidène)pyrrolo[3,2-d][1,2,4]-triazolo[1,5-a]azépine ; 10-(1-méthyl-4-pipéridinylidène)-10H-thiéo[3,2-d]-1,2,4-triazolo[4,3-a]azépine ; et 6,10-dihydro-10-(1-méthyl-4-pipéridinylidène)-5H-thiéo[2,3-d][1,2,4]triazolo[1,5-a]-azépine, de leurs stéréoisomères et de leurs sels d'addition pharmaceutiquement acceptables à un acide.

5. Composition pharmaceutique comprenant, à titre d'ingrédient actif, une quantité thérapeutiquement efficace d'un composé tel que défini à la revendication 1 et un support pharmaceutiquement acceptable.

6. Procédé de préparation d'une composition pharmaceutique selon la revendication 5, caractérisé en ce qu'une quantité thérapeutiquement efficace d'un composé selon la revendication 1 est mélangée intimement avec un support pharmaceutique.

7. Composé selon la revendication 1 destiné à être utilisé en tant que médicament.

8. Composé de formule

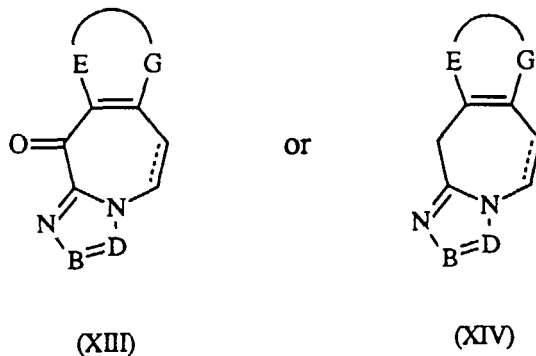


sel d'addition ou forme stéréochimiquement isomère de celui-ci,

dans laquelle chacune des lignes en pointillé, -E-G- et -B=D- sont tels que définis à la revendication 1;

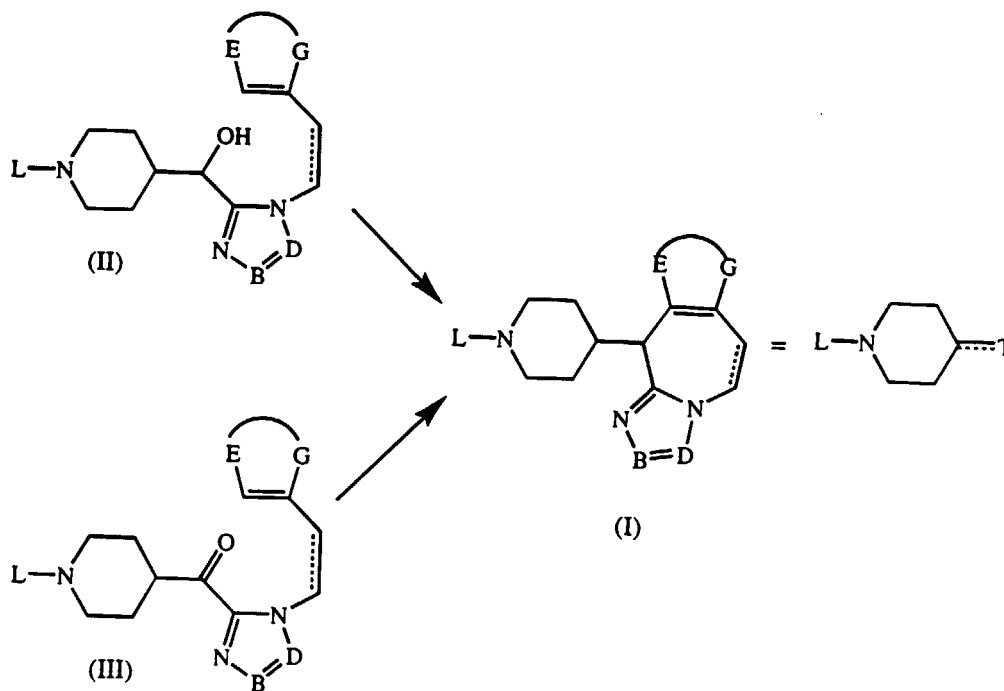
Q représente un C₁₋₆-alkyloxycarbonyle, un C₁₋₄-alkylcarbonyle ou un alkyle en C₁₋₆ substitué par un halogéno, un cyano, un amino ou un méthylsulfonyloxy.

9. Composé de formule



sel d'addition ou forme stéréochimiquement isomère de celui-ci, dans laquelle la ligne en pointillé, -E-G- et -B=D- sont tels que définis à la revendication 1.

10. Procédé de préparation d'un composé selon la revendication 1, caractérisé par la cyclisation d'un alcool de formule (II) ou d'une cétone de formule (III) en présence d'un acide ;



où chacune des lignes en pointillé représente indépendamment une liaison facultative, et L, -E-G- et -B=D- sont tels que définis à la revendication 1 ;

et en outre, si on le souhaite, la transformation des composés de formule (I) les uns en les autres en suivant des modes opératoires de transformation de groupes fonctionnels connus dans l'art ; la transformation des composés de formule (I) en une forme de sel par traitement avec un acide ou une base pharmaceutiquement acceptable ; ou inversement, la transformation de la forme de sel en base libre ou en acide libre par traitement avec un alcali, respectivement un acide ; et/ou la préparation de leurs formes stéréochimiquement isomères.